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The Etiology of Phrynoderma

Histologic Evidence

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PHRYNODERMA is the name given by Nicholls[1] to a condition of follicular hyperkeratosis of the skin occurring in malnourished individuals. It occurs in late childhood and adolescence. Occasionally it occurs in adults as well, but it rarely develops in infants. It manifests itself in the form of papular eruptions involving the pilosebaceous follicles, appearing as discrete thorny nodules, round and oval in shape and varying in diameter from the size of a pinhead to a split lentil. These occur initially on the posterior and lateral aspects of the arms and thighs and later involve the buttocks and back.

The condition is widely prevalent in the East. Frazier and Hu[2] first observed spinous papules at the site of the hair follicles in a group of Chinese soldiers. The condition was seen mostly on the extensor surfaces of the arms and occasionally on the outer parts of the legs and associated sometimes with dry dark skin. These workers further pointed out that the follicular lesions were most common in young adults and were associated with the typical signs of keratomalacia but not with signs of other vitamin deficiencies.

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Lowenthal[3] observed a similar condition in East Africa, and Nicholls[1,4,5] made independent observations in Ceylon. Subsequently, the condition was observed and studied by Goodwin[6] and Pemberton[7] in England, Youmans and Corlette[8] and Lehman and Rapaport[9] in the United States. In India, the condition had been observed and investigated by Aykroyd and associates,[10,11] Rajagopal, Chowdhury, and co-workers,[12–14] Gopalan,[15] and Menon *et al.*[16] From all available evidence, it may be presumed that phrynoderma is undoubtedly a condition arising out of a deficiency in diet.

Regarding etiology, this disease has frequently invited much controversy among nutritionists and dermatologists, and even now the exact mechanism of its pathogenesis is far from clear.

For several years after its first appearance in the scientific literature, workers in different parts of the world favored the idea that the condition was caused by vitamin A deficiency. This was based mainly on the experience of clinical response obtained after administration of fish liver oil rich in vitamin A. Frazier and Hu,[2,17] for instance, cured the condition by oral administration of 30 ml of cod liver oil daily as a supplement to a well-balanced diet. Lowenthal[3] found this condition in association with xerophthalmia and defective dark adaptation and reported that the condition was cured by treatment with 1 oz of cod liver oil a day with-

out any modification of diet. Nicholls[5,6] attributed it primarily to vitamin A deficiency in the diet but considered that deficiencies of other food factors might also be responsible. Goodwin[6] also shared the same view.

Rao[18] published the findings of histopathologic investigation of phrynoderma in humans. The salient features according to him were the following conditions: (a) the mouth of the follicle was completely sealed by dense mass of horny tissues, the surface of which was flush with the horny layer of the surrounding skin, (b) generalized surface keratosis, and (c) lymphocytic infiltration in the perifollicular area. This investigation led him to conclude that this condition was mainly caused by deficiency of vitamin A.

The nutrition survey carried out in Malabar (India) by Aykroyd and Rajagopal,[10] however, cast doubts on this concept of the etiology of phrynoderma. The amount of animal and vegetable fat (from fish and coconut) consumed by people of Malabar was relatively high compared with that in other parts of the province where phrynoderma was common. These investigators observed the rarity of phrynoderma among children in this area, although a high percentage among them had Bitot's spots and xerophthalmia. On the basis of these observations the authors suggested that phrynoderma might be due to deficiency of fat in diet and discounted vitamin A as a causative agent. Extension of the above work in boarding schools by Aykroyd and Krishnan[11] confirmed the findings of Aykroyd and Rajagopal[10] that there was no relationship between phrynoderma and intake of vitamin A and carotene. They commented that it was difficult for them to explain the incidence of this condition solely on the basis of vitamin A deficiency.

A diet survey in school boys was carried out by McIntosh *et al.*[19] who observed the incidence of folliculosis, said to be an earlier stage of follicular hyperkeratosis. The authors reported that in 38 cases, plasma vitamin A levels ranged from 39–147 I.U./100 ml, carotene from 44–228 I.U., and vitamin C from 0.05–0.3 mg/100 ml plasma, while in 80 normal boys of comparable age the corresponding figures were 29–197 I.U., 24–234 I.U., and 0–0.3 mg/100 ml. These findings indicated that there was no significant difference in vitamin A, carotene, and vitamin C content of plasma between normal individuals and persons suffering from folliculosis. These authors also administered vitamin C and vitamin A and showed that these vitamins had no beneficial effect on the skin lesions.

Krause and Pierce[20] in a survey of 399 children found no significant difference in vitamin A level of blood of children with or without folliculosis. The children of both groups were equally capable of absorbing vitamin A as indicated by the serum levels after the administration of 50,000 and 250,000 I.U. vitamin A. On the basis of clinical findings Gopalan[15] pointed out that phrynoderma was not due to deficiency of vitamin A and suggested that it might be due to a deficiency of fatty acids. Rajagopal and Chowdhury,[12,13] in an investigation carried out in this laboratory, indicated that essential fatty acids may play a very important role in the etiology of phrynoderma. They observed marked improvement by oral

TABLE I
Composition and Nutritive Value of Diet

	Quantity consumed per adult per day (oz)	
	Normal	Phrynoderma
1. Cereals (rice and wheat)	17	17.5
2. Pulses (lentils, black gram)	2.5	2
3. Leafy vegetables (spinach, amaranth)	4.5	5
4. Potato	2	2
5. Fish (small variety)	1	0.5
6. Jaggery (crude sugar)	1.5	1
7. Condiments (chilies, turmeric, coriander, mixed)	1	0.5
8. Mustard oil	1.25	0.75
NUTRITIVE VALUE		
Calories	2573	2512
Protein (g)	67.8	62
Fat (g)	44	27
Carbohydrate (g)	501	498
Vitamin A (I.U.)	4380	3500
Vitamin B_1 (mg)	1.4	1.2
Vitamin B_2 (mg)	1.1	0.88
Niacin (mg)	16.3	18
Vitamin C (mg)	79	82
Iron (mg)	32.6	24.2
Calcium (g)	0.4	0.36

TABLE II
Daily Intake of Essential Fatty Acids

Fatty acid	Quantity (g)	
	Normal	Phrynoderma
Linoleic acid	6.04	3.41
Linolenic acid	2.67	1.46
Arachidonic acid	0.02	0.03
TOTALS	8.73	4.90

administration of raw linseed oil and, simultaneously with the clinical cure, the serum lipids value and iodine number of fatty acids, which were lower than normal, attained the levels found in normal subjects. These observations were corroborated by Menon, Tulpule, and Patwardhan.[16]

Ramalingaswami and Sinclair[21] produced vitamin A and essential-fatty-acid deficiencies in two groups of albino rats and compared the histologic changes in the skin. In essential-fatty-acid deficiency, there was surface keratosis which increased in severity in the region of the opening of the hair follicle. The dense compact keratin layer closely plugged the follicular opening. In vitamin A deficiency, there was atrophy of the epithelium with loose hyperkeratosis. Instead of dense keratotic plugging, there was wide dilatation of the upper third of hair follicle with atrophic epithelium and loose hyperkeratosis. These workers[21] concluded that the histologic picture of the skin of rats in essential-fatty-acid deficiency resembled that of human phrynoderma in the human. Kolah and Rao[22] working on rats concluded that phrynoderma in the human might be due to combined deficiencies of vitamin A and essential fatty acids, vitamin A playing a major role.

In view of the conflicting ideas it was felt that a study of the etiology of phrynoderma in human subjects would be a fruitful line of investigation. In recent years, a considerable amount of work has been done on this problem,[12,13,15,16] presenting biochemical and clinical data as evidence before and after essential-fatty-acid therapy. Therefore, since there is no mention in the literature, so far, of a histologic investigation of this nature in human subjects, a study based on histologic observations was considered worthwhile.

EXPERIMENTAL

Selection of Cases and Clinical Examination

Clinical observations were made on 61 patients of both sexes, of ages ranging from 5 to 15 years, attending the outpatient department of the School of Tropical Medicine, Calcutta. The patients belong to the lower economic group. The general conditions of health of these subjects were poor, though some showed evidence of good health.

Dietary Intake in Phrynoderma and Comparison with Normal

In order to find out the nature of dietary

TABLE III
Serum Lipid of Normal Individuals and Subjects with Phrynoderma

Subject	No. cases	Serum lipids (mg per 100 ml)			Iodine number of fatty acids
		Total lipids	Total cholesterol	Total fatty acids	
Normal	45	485 ± 16.06	156 ± 10.00	329 ± 12.57	114 ± 1.22
Phrynoderma	61	422 ± 16.40	140 ± 6.52	282 ± 15.04	99 ± 2.9

TABLE IV
t Test of Significance Between the Means of the Groups

	Groups	Means	Difference in means	Stnd. error of difference	Degrees of freedom	*t*	Remarks
Iodine number	Normal vs. experimental	113.889 92.958	20.931	3.439	67	6.086	Significant
Fatty acid	Normal vs. experimental	329.130 282.460	46.670	14.253	67	3.274	Significant

intake, a diet survey lasting a week was carried out in 15 selected families of subjects with phrynoderma by the weighing method (weighing of raw foodstuffs). In order to compare the diets of subjects with phrynoderma with those of normal persons of identical socioeconomic environments, a diet survey was also carried out by the same method in 15 comparable families showing no cases of phrynoderma. The composition of the diet and the nutritive values are shown in Table I.

Essential Fatty Acid Content: The essential-fatty-acid content of the diets of phrynoderma cases as well as normal individuals were determined by extracting the total fat of the foodstuffs consumed daily and subsequent estimation of essential-fatty-acid content of the fat by spectrophotometric method of Mitchell, Kraybill, and Zschile[23] using the calculation mentioned by Beadle.[24] The daily intake of essential fatty acids of normal as well as phrynoderma subjects is listed in Table II.

Clinical Condition

It was found that more than 40 per cent of these cases had other types of nutritional disorders. The common manifestations of nutritional deficiencies associated with phrynoderma were cheilosis, glossitis, and angular stomatitis. Bitot's spots and blepharitis were present only in few of them.

Biochemical and Histologic Studies

The blood lipid content of the normal and phrynoderma subjects was determined. A fasting blood sample was drawn from the patients and serum was used for lipid analysis. Bloor's method[25] was used for the determination of total lipids and cholesterol content of blood serum and the micromethod of Yusuda[26] was adopted for the determination of iodine number of blood fatty acids.

Biopsy of skin from the elbows and thighs, the sites frequently affected, was done after procaine infiltration before starting the treatment. A second biopsy was taken after treatment from almost the same site. After fixation in buffered formalin saline, the tissues were transferred in polyethylene glycol (Carbowax, 4000) in three or four successive stages for dehydration, impregnation, and embedding. Sections of 6–8 μ thickness were cut and stained with hematoxylin and eosin. The sections were mounted in the usual way in Canada balsam.

Treatment

The subjects for this investigation were treated in two different groups:

(a) Raw linseed oil, $^3/_4$ oz per day, was given orally in two divided doses.

(b) Linoleic acid (B.D.H. technical grade), 1 teaspoonful per day, was given orally.

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Figs. 1 and 2. Effect of linseed oil therapy in phrynoderma. Fig. 1. Before treatment. Fig. 2. Same case as Fig. 1, after treatment for 16 weeks.

TABLE V
Effects of Treatment of Phrynoderma on Serum Lipids

Treatment	No. cases	Serum lipids (mg per 100 ml)			Iodine number of fatty acids
		Total lipids	Total cholesterol	Total fatty acids	
Linseed oil	24	53.80 ± 18.52	3.17 ± 6.79	50.63 ± 18.19	17.54 ± 7.76
Linoleic acid	6	18	1	17	13

TABLE VI
t Test of Significance on the Increase in Iodine Number and Fatty Acid by the Treatment

	Mean of the increase	Stnd. error of the mean	Degrees of freedom	*t*	Remarks
Iodine number	17.540	3.828	23	4.582	Significant
Fatty acid	50.630	9.097	23	5.566	Significant

It was considered unnecessary to select a third group of patients to be treated simultaneously with vitamin A on the basis of observations mentioned in the review of literature regarding the lack of correlation between vitamin A and phrynoderma. Moreover, in the present investigation the main object was to establish the role of essential fatty acids in the etiology of phrynoderma.

RESULTS

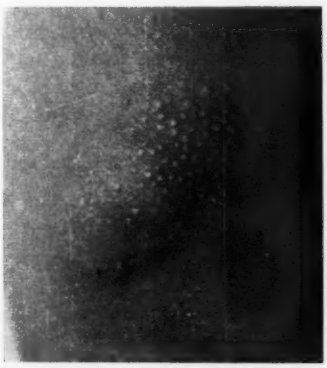
Clinical Effects

Clinical improvement was noticed after about four weeks of therapy in the patients treated with linseed oil. Complete cure was achieved after 16 to 20 weeks, depending on the severity of the condition. In the second group, in which linoleic acid therapy was adopted, complete cure was noticed much earlier (after 12 weeks of therapy). Figures 1 and 2 demonstrate the clinical effects of linseed oil therapy, and Figures 3 and 4 show the effects of linoleic acid therapy on some selected cases of phrynoderma.

Biochemical Determinations

Serum analysis of 45 normal individuals and 61 phrynoderma cases for total lipids, total cholesterol, total fatty acids, and iodine number of fatty acids is presented in Tables III and IV.

The levels of total fatty acid, cholesterol, and the iodine number of serum fatty acids of the selected patients of the two groups were estimated before any treatment was started. These were determined again after the dis-



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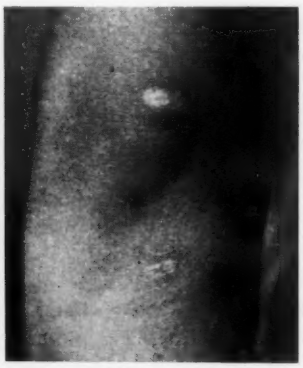

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Figs. 3 and 4. Effect of linoleic acid in phrynoderma. Fig. 3. Before treatment. Fig. 4. Same as in Fig. 3, after treatment for 12 weeks.

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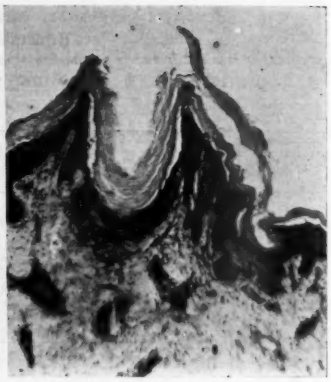

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Fig. 5. Histologic features of a phrynoderma nodule. (H & E; ×250) Fig. 6. Histologic features of phrynoderma nodules. (H & E; ×250) Fig. 7. Histologic features of skin in phrynoderma. (H & E; ×250)

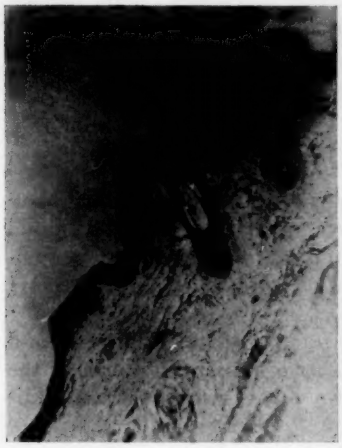

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Fig. 8. Histologic features of skin after treatment. (H & E; ×50)

Fig. 9. Histologic features of skin after treatment. (H & E; ×125)

appearance of the symptoms. The results of these analyses are presented in Tables V and VI. The number of cases treated with linoleic acid was small, due to unavailability of linoleic acid (technical grade, B.D.H.) and lack of proper cooperation on the part of the patients. As the cases were not sufficient in number, no statistical analysis was done on these figures.

Histologic Examination

Figures 5, 6, and 7 depict the different stages of the characteristic phrynoderma nodule from selected subjects. The histologic picture conforms to the typical description of phrynoderma given by Rao,[18] Frazier and Hu,[17] and Lowenthal.[3] Ramalingaswami and Sinclair[21] produced essential-fatty-acid deficiency in rats. The histologic picture of the skin in these rats included thickening of the stratum malpighii and granulosum layer, closely packed adherent keratin layer and hyperkeratosis around the opening of the hair follicles which plugs them. The histologic features observed in these subjects resembled very closely those described by Ramalingaswami and Sinclair,[21] with certain differences which are characteristics of the two species. There was an appreciable thickening of the stratum malpighii and granulosum and a very dense and compact keratin layer plugging the hair follicle. There

was also atrophy of the lining epithelium of the hair follicle.

In Figures 8 and 9 the histologic appearance of the skin from almost the same site is depicted after clinical cure was established by treatment with linseed oil and linoleic acid, respectively. There was complete regressive change in the epithelium and disappearance of the extensive keratinization. The structure of the pilosebaceous follicle and the perifollicular area resembled that seen in a normal healthy skin.

DISCUSSION

A considerable amount of work done in recent years served as clinical and biochemical evidence in favor of essential-fatty-acid deficiency as the cause of phrynoderma in human subjects. Ramalingaswami and Sinclair[21] from their histologic investigation on essential-fatty-acid and vitamin A deficiencies in rats pointed out the similarity in the features between human phrynoderma and essential-fatty-acid deficiency in rats.

In the present investigation opportunity was taken to perform a skin biopsy in a considerable number of clear-cut cases of phrynoderma, both before and after treatment with essential fatty acids. Simultaneously, biochemical data regarding blood lipids were also collected to support the clinical diagnosis and also to demonstrate the effects of linseed oil and linoleic acid therapy. Since the review of literature revealed that several authors[10,11,15,19,20] concluded that there was no correlation between vitamin A and phrynoderma, our biochemical investigation did not include the role of vitamin A along with essential fatty acids. Moreover, the results of diet surveys showed beyond doubt that there was not much difference in the total intake of carotene and vitamin A between normal persons and subjects with phrynoderma. On the other hand, there was significant difference in the total intake of essential fatty acid. The histologic features and biochemical data presented in this paper strongly support the hypothesis that human phrynoderma is a manifestation of essential-fatty-acid deficiency.

The data in Table III show a notable reduction in the iodine number of the fatty acids of serum of subjects with phrynoderma as compared to normal individuals. There was also a significant reduction in other fractions of serum lipids. Treatment with essential fatty acids, either as linseed oil or as linoleic acid, brought these values up to normal level. Simultaneously with these biochemical changes a clinical cure was observed.

The histologic features of phrynoderma in our subjects bear a close resemblance to those described by Ramalingaswami and Sinclair[21] in rats deficient in essential fatty acids. The effect of treatment with essential fatty acids on the histologic appearance of the skin in phrynoderma gives much stronger support to this new etiology. In our opinion, one should have no hesitation in describing phrynoderma as a manifestation of essential-fatty-acid deficiency.

SUMMARY

Clinical, biochemical, and histologic investigations were carried out on selected well-established cases of phrynoderma. The therapeutic effects of essential fatty acids in the form of raw linseed oil and linoleic acid were observed. Biochemical and histologic changes as a result of this therapy were studied. The significant role of essential fatty acids in the etiology of phrynoderma in human subjects has been discussed in the light of these evidences, and it is concluded that phrynoderma is a manifestation of essential-fatty-acid deficiency in man.

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Is Breast Feeding Best?

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THE PROPORTION of mothers who breast feed their babies has become steadily lower during the past few decades. In Britain, only about one mother in five now continues to breast feed until the baby is three months old. In America, only one in five is breast feeding at the end of the lying-in period.[1]

This decline of breast feeding has taken place in defiance of orthodox medical opinion. Most doctors and nurses are taught, and believe, that breast feeding is best. Nearly all pediatric textbooks extol the superiority of breast milk over artificial feeds, and some go so far as to say that breast feeding has all the advantages and no real disadvantage. In Britain, at least, breast feeding is advocated in nearly all maternity hospitals, and most local authorities encourage it through an increasingly elaborate organization of clinics and health visitor services.

The growing unpopularity of breast feeding among mothers suggests that this "natural" method of nourishing babies is not so trouble-free as it is said to be by authoritative medical teaching.

In this paper, I shall first examine some of the assumptions that appear to underly the medical point of view. Next, I shall refer to work recently undertaken to study breast feeding from the mother's point of view, which indicates that real disadvantages do exist.

HISTORICAL BACKGROUND OF THE MEDICAL ATTITUDE

About fifty years ago, there was widespread concern about the tremendously high infant mortality. In many industrial towns about one baby in four died before its first birthday, commonly from infection. It was considered with some justification that mortality was particularly high among bottle-fed babies. Standards of hygiene were very low, and furthermore, most of the feeding mixtures available about the beginning of this century were nutritionally inadequate. Morse,[2] reminiscing on forty years of infant feeding in the United States of America, stated that "most babies were fed on proprietary foods, a considerable proportion of which contained no milk and were mixed with water. Very few physicians had any idea what the mixtures contained, or would have understood if they knew." Early in the present century, elaborate attempts were being made to mimic what was known of the chemical composition of human milk, but this often made artificial feeding more difficult for the mother. Up to the time of the first World War, artificial feeding remained a dangerous and expensive art.

Under these circumstances, doctors were undoubtedly right to do everything possible to encourage breast feeding. But though the motives were excellent, the means were often dubious. Like all propaganda, the slogans used to promote breast feeding were categorical, leaving no room for doubt. For example:

"Every mother can breast feed her baby." This was sometimes put so that the onus fell squarely on the mother: "Every woman can breast feed if she wants to." "Breast milk is designed by Nature specially for the baby." "Breast feeding is safer than bottle feeding." "Breast feeding is cheaper than bottle feeding." Or, even, "Breast feeding costs nothing." These, or closely similar, examples are familiar even today.

Though, on the surface, the advocacy of the medical profession appears to have changed comparatively little during the past half-century, there may be an important difference between precept and practice. Many

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family doctors are by no means unwilling, on request, to prescribe estrogens for the suppression of lactation, and a breast-milk substitute for the infant.

The impact of official medical opinion upon the minds of mothers is no doubt greatly modified by the advertisements of manufacturers of foods for infants. Every child is aware, from an early age, of the pictures of bonny babies assiduously published by commercial firms. The effect is not greatly altered by such lip service to medical opinion as "Breast feeding is best, but when it fails, use———."

MATERNAL CAPACITY FOR BREAST FEEDING

Surprisingly little is known about variations in the yield and composition of breast milk. From many pediatric texts, it might be assumed that the composition of breast milk was relatively constant, and that the great majority of women can, if they wish, produce a sufficient yield.

In a recent study,[3] several hundred 24-hour specimens of breast milk were analyzed for protein, carbohydrate, and fat. The mothers were mostly primiparas, and the results indicated that about one-third were producing milk which was unsatisfactory in quantity or quality, or both, for the nourishment of the baby. This result is in accord with reports by Engel[4,5] that 30 to 40 per cent of recently delivered women examined at autopsy had breasts which were grossly deficient in secretory tissue.

There seem to be two main reasons for the fact that many women are incapable of an adequate lactation. First, the human infant has never been entirely dependent on his mother's lactational ability, because substitute mothers or substitute milks were always readily obtainable. Thus, there is little genetic selection for lactational ability. The evidence suggests that variations are much greater in man than in other mammalian species.

Second, the human mother frequently postpones childbearing and lactation until many years after she has attained sexual maturity. My data show clearly that both the quantity and the nutritive value of breast milk becomes less with increasing age in primigravidas. In 509 24-hour samples, the mean yield fell from 441 ml in women under 20 years of age to 313 ml in those of 30 or over, and the fat content fell from 3.25 g/100 ml to 2.83 g/100 ml. It is tempting to suppose that failure to use the mammary glands is accompanied by some process analogous to disuse atrophy.

It thus appears that, in modern Western society at least, a fairly high proportion of mothers are physiologically incapable of satisfactory breast feeding.

NUTRITIVE VALUE OF BREAST MILK

I have shown above that many women do not secrete milk of adequate caloric value for satisfactory infant growth. Even with a high yield, a milk with only 1.5 g of fat/100 ml is insufficient for any healthy infant.

Apart from such considerations, it is often argued that human milk has chemical or physical qualities which make it more suitable for infant nutrition than any nonhuman milk. In a general way, an "appeal to Nature" of this kind is plausible, but the intention is usually to imply that nonhuman milks are in some way chemically inappropriate for human infants, and I am not aware of any satisfactory demonstration that the substitute milks commonly used nowadays prejudice normal infant growth or general health. Many experienced doctors say that the breast-fed infant "smells sweeter" and has a "bloom" which is not shown by artificially fed babies. This may be so, but it would be difficult to prove, and no attempt seems to have been made to do so.

There is, indeed, some room for doubt that mother's milk is always best even when it is adequate in caloric value. The not uncommon case of the healthy breast-fed baby which cries persistently, apparently from colic, and is immediately "cured" when given a substitute milk, has been reported elsewhere.[6]

THE SAFETY OF BREAST FEEDING

That breast feeding is safer for the baby than bottle feeding has been, and to some extent remains, the keystone of arguments in favor of breast feeding. The argument was certainly true a few decades ago, but there is no recent

evidence which supports it beyond reasonable doubt.

The common finding that more bottle-fed than breast-fed babies die in epidemics of gastroenteritis is often used in evidence. But the assumption is that the bottle-fed and the breast-fed groups differ only in their method of feeding. In Britain, bottle feeding, and particularly careless bottle feeding, is practiced most widely by mothers in the lowest socioeconomic groups.[7,8] It is in these groups, where standards of hygiene are least satisfactory, that intestinal infections are most likely to spread and most deaths likely to occur.

If bottle feeding is indeed notably more dangerous than breast feeding, it is surprising that the decline in breast feeding has been accompanied by such a great reduction of infant mortality, In Bristol, for example, the breast feeding rate at 3 months fell from 76 per cent in 1929 to 36 per cent in 1949;[9] during the same period the infant mortality rate fell from 60 to 26. It is not, of course, suggested that the infant mortality has fallen *because* there is less breast feeding; but the figures do show that an appeal to the safety of breast feeding is now difficult to sustain.

COST OF BREAST FEEDING

Breast feeding is by no means "free," or even very cheap. The metabolic costs can be readily calculated, and these must ultimately be paid for in cash or kind.

The average breast-fed baby growing from, say, 3.5 kg at birth to 6 kg at 3 months, requires 400-700 calories daily from the mother's milk. Given an efficiency of production of 80 per cent (unpublished data) the mother utilizes about 100 calories for every 80 calories secreted as milk. She must therefore expend, *in addition to her ordinary energy output*, about 500 calories daily at the start of lactation, rising to about 900 calories by the end of the third month.

The cost of food which will provide about 900 calories daily varies widely from country to country, and within each country, but in Western countries at least this cost is much greater than that of cow's milk fed directly to the baby. This is not unreasonable; the mother has to eat readily digested food to produce her own milk, whereas the cow, with considerable physiologic skill, can utilize pasture.

However, it is understandable that breast feeding may well *appear* to be cheaper than bottle feeding, which has to be paid for in cash at the time. Many breast-feeding mothers probably succeed in reducing their ordinary activities to some degree, and may subsidize lactation by breaking down body tissues. A tendency to storage is a feature of normal pregnancy, but it is doubtful if such normal stores would contribute more than about 200 calories/day toward lactation. When they have been expended, many mothers will be capable of imposing further drains on their own tissues, though possibly at some cost in vitality and health. Clinical observations suggest that the appetite during lactation is not much greater than during pregnancy, so that the mother may be under the impression that, because she does not buy more food, she is producing breast milk at little or no extra cost. In fact, the financial cost is being spread out, or is being paid in kind, usually temporarily, by a loss of body weight.

PSYCHOLOGIC VALUE OF BREAST FEEDING

The repose and contentment of a successful breast-feeding mother has an appeal which has inspired artists for centuries, and has also been exploited in breast-feeding propaganda. In recent years the importance of the mother-child relationship to mental health has been stressed, and the act of breast feeding undoubtedly expresses this relationship in its most appealing physical form.

I am not competent to debate whether breast feeding favors the future mental health of the child more than does bottle feeding, but there is at present no scientific evidence to support this view. At the very least, a long-term follow-up study of breast-fed and of bottle-fed infants, whose environment is alike in all other respects, would be required.

Breast feeding is also stated to confer psychologic benefits on the mother, and undoubtedly some mothers obtain a unique

pleasure from breast feeding. But extensive follow-up studies in Aberdeen (Scotland) show that this is by no means universal. Many denied vigorously that breast feeding was any more pleasurable than bottle feeding. As indicated below, questions about breast feeding seemed to conjure up for the majority memories of physical restriction, tiredness, worry, and even of pain.

MOTHERS' EXPERIENCE WITH BREAST FEEDING

Since most mothers have been conditioned to believe that "breast feeding is best" in the eyes of doctors, it is by no means easy to get them to discuss the subject without restraint at an interview conducted by a doctor or nurse. We have had to take elaborate measures to obtain information indirectly, or to make it clear to the mother that we did not seek to influence her attitude toward breast feeding but were genuinely interested in what her experience had been and what she really thought.

The findings in a follow-up study have been published elsewhere.[10] In brief, of 106 primigravidas who left the hospital fully breast feeding, and who were visited regularly at home until the baby was 3 months old, only two seemed to breast feed throughout this period without the slightest difficulty or complaint. It is probably significant that both these were living with their own mothers and had practically nothing to do except feed the baby and assist with its management.

The great majority of the breast-feeding mothers complained of feeling excessively tired. This is hardly surprising: Breast feeding is very exacting for a mother without domestic help. She must spend some 6–8 hours daily feeding the baby and catering to its other needs; at the same time, she must continue her responsibility for domestic management, the preparation of meals at fixed times, and shopping. With a new baby, visitors and visiting may be frequent. The physical strain is increased by the fact that, during the first few months, sleep is likely to be interrupted after about four hours. The active and lactating mother has to eat and drink more than usual; otherwise she will lose weight.

As expected from epidemiologic evidence previously obtained, two-thirds of the mothers studied gave up breast feeding during the study period. To quote from the report cited above, "... most mothers who have given up breast feeding are emphatic that when the baby was given bottle feeds he slept better, cried less, required less attention and was generally healthier, and that they themselves felt less tired and harassed and more confident."

In addition to this study, we have interviewed nearly 300 mothers five years after the first child was born. The interviews included questions on experience with infant feeding and these led on to more general discussion of the pros and cons of breast or bottle feeding. There was a small minority of satisfied breast-feeders and many who breast fed despite considerable ill-health and difficulty because they believed that "breast feeding is best." But the great majority had turned to the bottle—usually quite soon after leaving the hospital—and were quite unrepentant.

It is perhaps necessary to explain that many mothers are incapable of explaining retrospectively exactly *why* breast feeding was not a success. The circumstances are usually inherently complicated, with perhaps an ailing infant, a tired mother, domestic harassment, prolonged doubt as to what is really best, and a great deal of conflicting advice. Invited to explain, the mother often says merely, "My milk went away, so I put him on the bottle." It needs much time and patience to go further; and even then reliable information is usually lacking on such crucial questions as the yield and quality of the milk and the weight gain and clinical state of the infant.

Some attitudes of infant feeding derive from the conditions of modern life. For example, privacy is now considered to be essential for breast feeding; we found that many mothers were unwilling to put the baby to the breast even within the family circle. By no means all mothers have a private and heated room to retire to every few hours; and if they have, the need for privacy often conflicts with social requirements when visitors are about or the mother goes visiting.

Medical teaching has, perhaps unwittingly, given the mother a strong argument for bottle feeding through its insistence on "formulas" and "normal" gains of weight. Mothers often told us, with an air of stating the obvious, that a great advantage of bottle feeding is that "you can see what he's getting." Apparently an empty breast and a sleeping baby are no longer enough for peace of mind.

It may seem at first sight curious that a natural function such as breast feeding should be attended by so much difficulty, but the defects of breast feeding seem to result from the mother's environment at least as much as from faults in the lactational mechanism. The pressures and needs of modern civilization may be mainly responsible. In primitive society, standards of infant care are far less exacting (judging by the death rates, at any rate); the mother can rely on the family group to relieve her of most responsibilities additional to care of the baby; she can put the baby to the breast whenever it seems hungry; and since she knows of no other kind of feeding, there is no conflict of choice.

CONCLUSIONS

The above is liable to be construed as an attack upon breast feeding. It is therefore necessary to state explicitly that in my experience (both as a doctor and as a father) *satisfactory* breast feeding is by far the simplest and best of all the methods of infant feeding.

The difficulty is that many mothers do not find breast feeding satisfactory, and medical propaganda of classic type is clearly failing in its purpose as well as ignoring some biologic and human realities. What should be the attitude of the medical and nursing professions?

As a general basis, it seems reasonable to retain the slogan that breast feeding is best; but this should not be used as a war-cry to frighten mothers who are clearly unable or unwilling to breast feed, and there should be no implication that modern artificial feeding, properly conducted, gives unsatisfactory results. Each mother should be encouraged to try breast feeding, on the understanding that no blame will attach to her if the attempt fails. Under present conditions, many mothers carry an unnecessary load of guilt because they stop breast feeding under the shadow of direct or implied medical disapproval which has failed to understand the mother's point of view. Perhaps even worse, some mothers persist in breast feeding when from every rational point of view they should have abandoned it. An illustrative case is recounted elsewhere.[10]

If breast feeding leads to difficulties which are not easily surmounted, or if the mother is clearly unwilling to breast feed, she should be helped to feed the baby effectively by artificial means. Where the routine of teaching mothers in the hospital or in the home is concentrated almost exclusively on breast feeding, the mother who, by choice or necessity, has to bottle feed, may be unwisely neglected. It is surely true that good bottle feeding is preferable to inadequate breast feeding; and since the technic of bottle feeding is on the whole more exacting than that of breast feeding, it should be taught when necessary with equal enthusiasm.

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Coronary Heart Disease and Cerebral Vascular Disease in the South African Bantu

Examination and Discussion of Crude and Age-Specific Death Rates

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AT A CONFERENCE on "Hormones and Atherosclerosis," held at Brighton, Utah, questions were raised concerning *age-specific* death rates as against *crude* rates from coronary heart disease and cerebral vascular disease among the South African Bantu. These people often have been cited as an example of a population among whom coronary heart disease presents no public health problem; however, cerebral vascular diseases—softening and hemorrhage—certainly occur among them, although exacting a mortality rate lower than that prevailing among white populations.[1–6]

The diseases in question affect primarily the middle-aged and elderly. The Bantu, as we will show, are a comparatively "young" population. What will be the effect of this feature on the relevant mortality pictures, and moreover, how reliable are these pictures? In addition to seeking to answer these questions, it is proposed to make certain suggestions for future research to remedy the inadequacies of present knowledge.

RELATIVE YOUTHFULNESS OF THE SOUTH AFRICAN BANTU POPULATION

Data given in Table I were calculated from information provided by the local Department of Census and Statistics[7] and the *Demographic Yearbook*.[8] The table amply demonstrates the comparative youthfulness of the Bantu. The effect of this characteristic on the relevant death rates will now be estimated.

MORTALITY FROM CORONARY HEART DISEASE

Classifications of Coronary Disease

Table II provides data on crude and age-specific death rates from diseases included in groups 420 and 420–422 in the International List of Causes of Death. Both these groups have been used in publications dealing with the subject under discussion.

Group 420 variously is taken to denote arteriosclerotic heart disease; arteriosclerotic heart disease, including coronary disease; or arteriosclerosis of the coronary arteries. For clarification, it may be of value to quote Mann, who, in his paper bearing on diet and epidemiology of coronary heart disease,[9] states:

> Coronary heart disease will refer to diseases of the heart caused by limitation of blood supply to the myocardium resulting from disease of the coronary arteries. Coronary heart disease must include some instances not caused by atherosclerosis of the coronary arteries, but these are presumed rare and not a cause of important error. Coronary heart disease is primarily a clinical diagnosis and comprises angina pectoris, which is a highly uncertain and subjective diagnosis, myocardial infarction, coronary occlusion (i.e. death with coronary artery lesions but without signs of infarction) and myocardial fibrosis not attributable to causes other than chronic myocardial ischemia.

Group 420–422 (also known as B.26), in

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TABLE I

Age Distribution of Populations

Population or country	Age 45–64 years (%)	Age over 65 years (%)
Johannesburg urban Bantu	10	2
South African whites	17	7
Japan	15	5
Canada	18	8
New Zealand	19	9
U.S.A. (total population)	20	8
Sweden	23	10
England and Wales	24	11
France	25	12

addition to 420, includes chronic endocarditis not specified as rheumatic (421) and other myocardial degeneration (422). The group 420–422 was regarded by Yerushalmy and Hilleboe[10] as most specifically relevant to the problem under investigation, particularly in view of certain anomalies in the data relating to Italy and Japan.

We have not included the classification 430–434 (B.27), which includes other diseases of the heart, since idiopathic heart disease not due to coronary artery disease is frequently encountered among the Bantu.[11–13]

Sources of Information

Data on the Bantu relate exclusively to Johannesburg Bantu, and were calculated from information obtained from the Department of Census and Statistics[7] and from the Johannesburg Public Health Department.[14] All other data have been calculated from the following sources: *Demographic Yearbook*,[8] *Whitaker's Almanac*,[15] and *Epidemiological and Vital Statistics Report of the* WHO.[16,17]

For the Johannesburg Bantu, mean values for 1953–1956 are given. The other data refer to specific years between 1951 and 1954, mainly to 1953 and 1954.

For the different population groups, the mortality pictures during the periods 45–54 years of age plus 55–64 years of age differ quantitatively, but not qualitatively, from data for 45–64 years; figures for the latter period only are given.

Comment on Death Rates

Table II reveals a number of anomalies in the

TABLE II

Annual Mortality Rate of Coronary Heart Disease per 100,000

Population or country	Classification 420		Classification 420–422	
	Crude rate	Specific rate for 45–64 age group	Crude rate	Specific rate for 45–64 age group
Johannesburg Bantu	10	45	11	47
Whites	155	286	225	310
U.S.A. (total population)	226	370	275	410
Canada	171	309	225	349
New Zealand	150	261	254	313
England and Wales	141	163	299	205
Norway	80	93	138	120
Netherlands	67	93	147	128
France	38	54	51	60
Italy	26	45	156	185
Japan	10	25	41	85

figures on the different white populations, in regard to both crude and age-specific death rates, and also in regard to the classifications used. It is not proposed to discuss these anomalies, first because the burden of the paper is not affected by them, and secondly because we are concerned primarily with the situation among the Bantu. Assuming for the moment that the data given are reliable, it will be apparent from Table II that (1) whereas crude mortality from coronary heart disease among the Johannesburg Bantu is about one twentieth of that of the local whites, the Bantu mortality rate at 45–64 years is only a seventh of that of the local whites; (2) at 45–64 years the figure for the Bantu roughly is of the same order as that in France, Italy (only if 420 classification is used), and Japan; (3) a further point which emerges is that whereas France has a more aging population than the United States, mortality from coronary heart disease in France is far lower than that in the United States.

Reliability of Mortality Data

The first and foremost question is, what credence, if any, can be attached to the data on the Bantu? The limitations inherent in attempting to draw conclusions from death certificates are well appreciated. Even in a country such as the United States, gross differ-

ences (twofold) in mortality rate, not completely explicable, have been noted between various states;[18,19] furthermore, Mann,[9] in his critical examination, has reached the startling conclusion that "the available evidence indicates that the increase in coronary heart disease revealed by vital statistics is largely artificial." If serious misgivings obtain with data from a country like the United States, the question naturally arises as to what precisely is the position in countries where far less favorable conditions prevail for securing the information in question?

Among the Bantu, death certificates are required only in certain of the larger centers of population, and even there, it is questionable whether more than 90 per cent of deaths are reported. Many factors militate against obtaining accurate death certificates: the migrant character of the Bantu; the frequent uncertainty of these people of their exact age; the tendency of many doctors with little experience of disease among them to assume that sudden death, as in white people, is due to coronary heart disease; and so forth.

Necropsy Data: Dealing first with accurate sources of information, i.e., necropsy data, the most careful recent study is that of Higginson and Pepler.[3] At Baragwanath Non-European Hospital (1,500 beds), in 1,328 postmortems, on 807 males and 521 females over 20 years of age, there were 4 deaths in each sex from coronary heart disease; total mortality from this cause therefore was 0.6 per cent. At the same hospital[20] in 1954 and 1955, among 1,500 deaths of patients over 12 years of age, 11 (0.7 per cent) were certified as due to coronary heart disease, postmortem examinations being made in approximately one-third of these cases. Among the total Bantu population of Johannesburg (i.e. about half a million), between 1953 and 1956 there was a mean of 6,250 deaths annually, of which 45 were certified as being due to coronary heart disease, which was thus responsible for 0.7 per cent of total deaths, or 1.3 per cent of deaths over the age of 20 years. These figures for the total population provide a mortality rate far higher than would be expected on the basis of local hospital practice.

It is thus clear that although the mortality position in the Johannesburg Bantu hospital population may be regarded as reasonably accurate, the position among Johannesburg Bantu as a whole is far less certain. We know still less about rural Bantu who we suspect are even less susceptible to death from the disease than are urban dwellers. The limitations to our knowledge, while understandable, are a handicap.

Dietary Fat and Mortality in Urban Bantu: In the following populations, according to Yerushalmy and Hilleboe,[10] the proportion of calories derived from fat is, very approximately: French, 29 per cent; Italians, 21 per cent; and Japanese, 8 per cent; the figure for urban Bantu is about 15–20 per cent.[21] Yet, coronary heart disease mortality, although certainly low, appears to be roughly of the same order in the 45–64-year age groups of these various populations with their different contexts of diet and manner of life (perhaps the Italians should be excluded from consideration due to anomalies apparent in Table II). At first sight, for these four populations, this obvious lack of association between fat intake and coronary-heart-disease mortality (discounting for the moment errors inherent in the small numbers involved) would seem to underline still further the misgivings expressed in recent critical papers.[9,10,22]

But the inference regarding the lack of association with the Bantu may be wholly wrong. All urban Bantu are undergoing, in varying measure, "westernization" of diet and manner of life. Conceivably, therefore, many—indeed, perhaps all—of the urban Bantu certified as dying from coronary heart disease may have been living not on their traditional diet but on a diet similar to that of local white persons. To add force to this view, it may be recalled that Trowell and Singh,[23] among 6,500 necropsies of Kampala Africans, noted only one subject dying from coronary heart disease; but *he* was an African judge, obese, and living a "westernized" life.

Not only is it necessary to know accurately how many Bantu die from coronary heart disease, but it is equally necessary to learn all that is possible about the antecedents, clinical

history, nutrition, metabolism, pathology, and so on, of these patients.

Ryle[24] stressed that the study of the fit should not lag behind that of the unfit. In the present instance the extreme has been reached whereby a large amount of relevant information is available on Bantu in outward good health, virtually all of whom will not die from coronary heart disease; yet our knowledge of the few Bantu who *do* die from this cause is negligible. In other countries, however, where mortality from coronary heart disease is low, e.g. France, surely there is as great a need to know more about both unaffected and affected portions of the population. Thus, if the French population generally, i.e. the unaffected portion, do not have low serum cholesterol levels, we wonder whether the present intense endeavors among many white populations to lower cholesterol values in the hope of warding off death from coronary heart disease will be significantly rewarding.

Securing Accurate Information on the Bantu: It is clear that if study of the Bantu is to contribute knowledge of value on the etiology of coronary heart disease, we must have much more accurate mortality and other data on them than are available at present. What are the possible means of securing the information desired? The excellent long-term studies now being undertaken by Patterson and coworkers[25] at London, Ontario, on inmates of institutions would be impracticable on the Bantu, since far too many inmates would be needed to obtain even two or three autopsies of patients dying from coronary heart disease. The same difficulty applies to extensive studies on random population groups of the type undertaken, for example, at Framingham,[26] Albany,[27] and Los Angeles,[28] for to find even two or three Bantu developing or dying from coronary heart disease over a period of two to three years would require observations on very many thousands of people.

Quite apart from reasons of finance and organization, the migratory propensity of the Bantu, even in urban areas, almost precludes the carrying out of such studies, for investigations even of relatively short duration (e.g. pregnancy) occasionally have had to be abandoned for that very reason.

There would seem to be two fairly straightforward means of investigating Bantu known to have coronary heart disease. First, there are patients who have recovered from an acute coronary episode. In Baragwanath Hospital, annually there may be 10–20 patients admitted for coronary heart disease, of whom less than half die. This method at its best would provide only a very few patients suitable for intensive study. The second source of Bantu patients with coronary heart disease may be afforded by extensive electrocardiographic (ECG) studies. On this subject Mann[9] states:

> . . . this (electrocardiographic evidence) is objective and almost always unequivocal. Without this evidence it is doubtful that epidemiologic analysis could be applied to heart disease statistics. It is unfortunate that many population studies of coronary heart disease, especially when carried out in medically undeveloped areas, have not made better use of this most decisive evidence of the existence of the disease.

The ECGs of apparently healthy Bantu often show striking peculiarities of the S-T segment and T wave, but no pathologic Q waves. In the occasional patient suffering from myocardial infarction, the typical ECG changes of that lesion are clearly recognizable.[29] Given adequate resources, there should be no insuperable difficulty in carrying out ECG studies on large numbers of Bantu adults, especially the elderly, in order to isolate the small number with infarction. Very few examples will be found, but at least we will begin to learn whether the Bantu who suffer or die from this cause were living in a somewhat primitive, or in a partially or wholly westernized, manner. Conceivably no Bantu pursuing their traditional diet and manner of life die from coronary heart disease.

For etiologic research on coronary heart disease, the need for knowledge on the Bantu in both these respects, the number and the characteristics of those dying, is obvious.

MORTALITY FROM CEREBRAL VASCULAR DISEASE

Table III provides information on crude and age-specific death rates from diseases included in classification 331 and 332, and 330–334 (also known as B.22) in the International List

TABLE III

Annual Mortality Rate of Cerebral Vascular Disease per 100,000

Population or country	Classification 331–332		Classification 330–334	
	Crude rate	Specific rate for 45–64 age group	Crude rate	Specific rate for 45–64 age group
Johannesburg				
Bantu	26	98	29	108
Whites	66	112	73	128
South African whites	75	110	82	121
England and Wales	140	96	155	111
Japan	122	256	129	271
France	116	99	146	124
Italy	97	88	128	117
U.S.A. (total population)	91	109	106	127
New Zealand	91	112	105	132
Canada	80	90	95	105
Netherlands	76	57	94	68
Norway	62	41	123	77

of Causes of Death. Group 330 denotes subarachnoid hemorrhage; 331, cerebral hemorrhage; 332, cerebral embolism and thrombosis; 333, spasm of cerebral arteries; 334, other and ill-defined vascular lesions affecting the central nervous system.

Sources of data are the same as those for coronary heart disease (Table II).

Comment on Death Rates

Assuming for the moment that the figures given in Table III are reliable, then whereas the Johannesburg Bantu crude mortality rate is just under a third of that among the local white population, the mortality rate among the Bantu from 45–64 years is of the same order as that of many of the white populations given, and is higher than that of Netherlands and Norway.

As with Table II, Table III reveals certain anomalies between crude and age-specific rates, and between the classifications used. It is not proposed to touch on these anomalies since here again, the burden of the paper is not affected by them.

Reliability of Data

The limitations already discussed concerning accuracy of mortality data from coronary heart disease also apply in measure to mortality information on cerebral vascular disease. Thus, in Britain, Bull[30] has stated "it is reasonable to suppose that most doctors signing death certificates all over England and Wales have difficulty in giving the Registrar General an accurate picture of the cause of death following a 'stroke.'" Bull also emphasizes that many cerebral tumors may be hidden in the figures given for "hemorrhage" and "embolus and thrombosis." Turning to a different population, the Japanese, Keys[31] maintains that some of the numerous deaths from cerebral vascular disease in that country undoubtedly are erroneously diagnosed, death being due to coronary occlusion or ruptured syphilitic aneurysms of the aorta.

Information on the Johannesburg Bantu additional to that given in Table III is as follows. At the Baragwanath Hospital, in Higginson and Pepler's[8] series of 532 necropsies of patients over 20 years, 70 of the deaths (13.1 per cent) were from cerebral vascular disease. At that hospital,[20] from 1951 to 1955, according to death certificates and excluding deaths among children, cerebral hemorrhage, thrombosis, and embolism accounted for 6.1 per cent of deaths, and total cerebral vascular lesions, for 7.2 per cent of deaths. In respect to Johannesburg Bantu as a whole, in 1954, according to certificates, mortality from groups 331 and 332, and 330–334 accounted for 2.5 and 2.8 per cent, respectively, of total deaths and 4.5 and 5.1 per cent, respectively, of deaths of patients over 20 years. Concerning distribution of lesions at Baragwanath Hospital in 1955, 20 deaths were certified as from subarachnoid hemorrhage, 40 from cerebral hemorrhage, and 34 from thrombosis and embolism. Among total deaths of Johannesburg Bantu in 1954, 25 were from subarachnoid hemorrhage, 93 from cerebral hemorrhage, and 36 from thrombosis or embolism.

How reliable is the picture delineated by the information given? Local physicians have the impression that it provides a fair representation of the mortality situation prevailing, although the obvious need for more accurate data is stressed. There is little doubt that in urban and possibly in rural areas also,[5] cerebral

vascular disease (in particular, cerebral hemorrhage) is a formidable cause of death among these people.

Further Research on the Bantu

Among the Bantu, atherosclerosis of the cerebral arteries is common and occasionally severe.[5,6] The commonness of hypertension has often been reported.[32–33] If the figures given for mortality from cerebral vascular disease are valid, the question arises as to why our local Bantu are so prone to succumb from this cause. Why are cerebral vessels affected more than coronary vessels by atherosclerosis? Why has hypertension apparently more influence on cerebral vascular disease than on coronary heart disease? Among rural Bantu groups there are many differences in diet, salt intake, manner of living, and so on; we believe that determining whether differences occur in cerebral vascular disease among appropriately differing Bantu population groups possibly may shed some light on the reasons for the Bantu being so liable to die from this cause.

SUMMARY

It is widely accepted that the South African Bantu very seldom die from coronary heart disease, but that cerebral vascular disease constitutes an important cause of death. How valid are these beliefs? Since the diseases mentioned primarily affect the middle-aged and elderly, and since the Bantu are a relatively *young* population in contrast to *aging* white populations, specific mortalities from 45 to 64 years have been calculated for certain Bantu, and for a few white populations for comparison.

Calculations suggest that mortality from coronary heart disease among Johannesburg urban Bantu in the 45–64-year age group, according to death-certificate data (assuming for the moment that such are valid), is, although still much lower than among most white populations, roughly of the same order as that in corresponding French, Italian, and Japanese population groups. Hence, for comparative purposes and when dealing with populations such as the Bantu, the importance of knowing age-specific as well as crude mortality rates for this disease will be obvious. Regarding the accuracy of these rates, whereas the mortality picture among the Johannesburg Bantu hospital population probably is reliable, that among the total urban population is far less certain. Still more uncertain is the position in rural areas, where deaths from this cause are believed to be very infrequent. Apart from the need for more exact knowledge of the mortality picture, it is evident that the large amount of information now available on Bantu unlikely to die from coronary heart disease must now be matched by the far more difficult task of securing antecedents as full as possible on those who do die, to learn whether affected persons were pursuing a traditional, partially, or fully westernized manner of life. Until all the combined information is available the full value of the Bantu for etiologic research will not be realized.

Calculations also suggest that for Johannesburg Bantu in the 45–64-year age group, mortality from cerebral catastrophes actually is as high as that in most white populations, and that from cerebral hemorrhage probably is higher. While it is uncertain whether this mortality picture in the Bantu is accurate quantitatively, there is no doubt that cerebral vascular disease among them is a very important cause of death. The reason why these people are so prone to die from this cause is not clear. It is suggested that study of the relevant mortality in Bantu regional groups known to differ significantly in diet, salt intake, and blood pressure may throw some light on the subject.

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Indirect Indicators of Muscle Mass in Malnourished Infants

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ALTHOUGH protein malnutrition is probably the commonest deficiency disease in most parts of the world, it is difficult to advance beyond vague generalities until some method has been found of assessing the severity of protein depletion. As has been pointed out,[1] it is as if anemias were studied without any measurements either of hemoglobin concentration or of hematologic indices.

Several workers have attempted to establish criteria for the recognition of mild and early cases of kwashiorkor (so-called prekwashiorkor); from the public health point of view this is indeed an urgent problem.[2] Various signs have been suggested as characteristic, e.g. dyschromotrichia,[3,4] and arrest of bone growth.[5,6] These, however, are in the nature of associated phenomena and do not give any direct measure of the degree of protein depletion. In field studies the most useful single measurement is still that of body weight.

In severe hospitalized cases of protein malnutrition it has been shown that there is a large loss of protein from several organs. The total circulating plasma protein is reduced, in spite of a relative increase in plasma volume;[7] tissue analyses, both in vivo and after death, indicate that liver and muscle may lose up to 50 per cent of their cytoplasmic protein.[8,9,10]

Studies of this kind, however, cannot easily be extended to patients with mild protein malnutrition who are not in the hospital. Experience has shown that plasma protein concentration is not an early or sensitive index of protein depletion. A clear-cut reduction seems only to occur at a late stage, presumably because circulating proteins are maintained at the expense of tissue proteins.[11] This has been confirmed by a recent study of plasma pseudocholinesterase, an enzyme whose activity usually runs parallel with plasma albumin concentration. No difference in plasma cholinesterase activity was found in groups of children who were known to differ widely in their nutritional status.[12]

The results obtained on muscle biopsies suggest that in malnourished babies the deficit in body weight underestimates the degree of protein loss from muscle.[10] Since muscle is the largest protein-containing organ in the body, any index of muscle mass should give useful information about the extent of protein depletion.

It has long been supposed that creatinine output is a measure of muscle mass. Recently Miller and Blyth[13] have shown in a group of adults that there was a good correlation between 24-hour creatinine excretion, basal oxygen consumption, and lean body mass, as measured by specific gravity. Arroyave and his colleagues[14] found a significantly lower creatinine excretion in a group of Guatemalan children of low economic status as compared with controls.

The measurements reported here were made on infants in the hospital with the object of establishing their value for use in the field. The aims were, first, to compare creatinine excretion with body-weight deficit as an index of depletion. Secondly, since 24-hour urine collections are not easily made outside the hospital, we have tried to find whether any useful information about muscle mass could be obtained by simple somatometric measurements.

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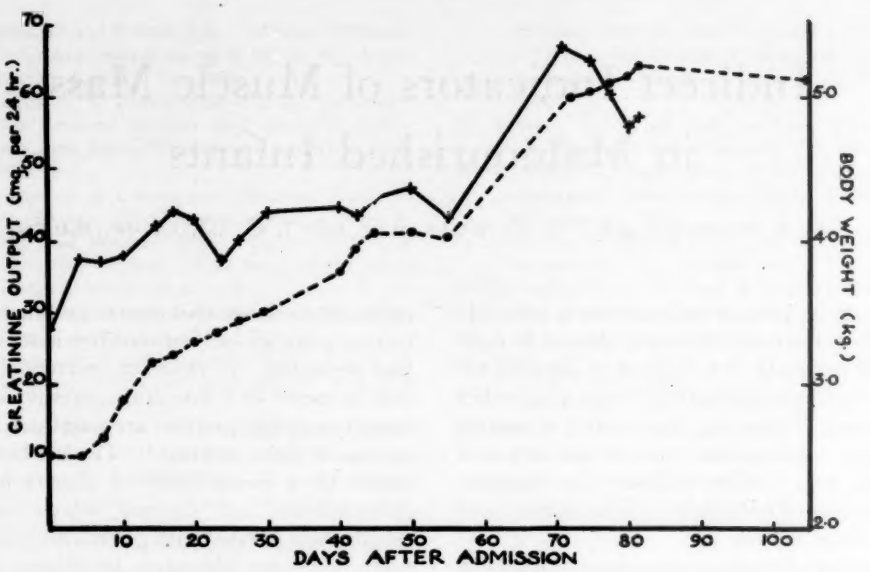

Fig. 1. Increase in body weight (● - - - - - ●) and in creatinine output (+ ——— +) in a malnourished infant during treatment.

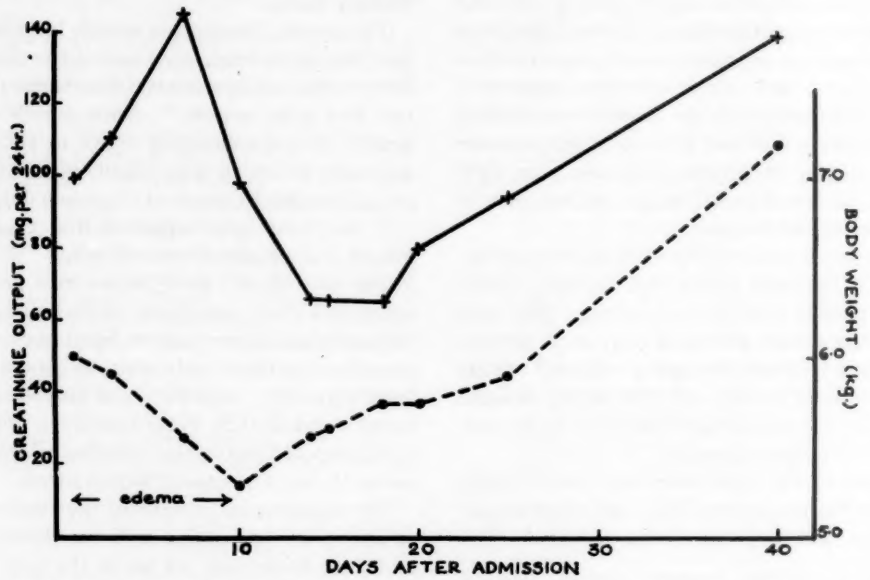

Fig. 2. Increase in body weight (● - - - - - ●) and in creatinine output (+ ——— +) in a malnourished edematous infant during treatment.

CLINICAL MATERIAL

Thirty-four malnourished babies, ranging from 3 to 20 months of age, were studied. Clinically they conformed to previous descriptions from Jamaica.[15,16] The series contained at one extreme examples of typical kwashiorkor, with hepatomegaly, edema, and well-preserved subcutaneous fat, and at the other extreme

cases of pure marasmus. Most common was the intermediate type of case described by Jelliffe[16] as marasmic kwashiorkor.

For the present purpose we do not consider these clinical distinctions very important. All the babies were protein-depleted; they differed in the extent of subcutaneous-fat loss and body-weight deficit below the normal weight for the age. These differences are probably related mainly to the level of previous caloric intake and to the duration of the malnutrition.[17]

Balance studies were done on many of the babies for varying periods after admission. The results of these will be reported separately. A number of different diets were used for treatment, and in most cases the diet was changed from time to time during the baby's stay in the hospital in order to assess the effect of altering the protein and calorie intakes. Some babies were fed for varying periods on pooled human milk; others were given diets based on dried skimmed milk with added oil (peanut or olive oil), sugar, or precooked starch to increase the caloric value. Most of these mixtures contained either 1.1 or 2.1 g protein per 100 ml. A few babies were given a mixture containing 4 g protein per 100 ml. The creatinine results have not been analyzed separately in relation to the different diets because, as will be shown, no relationship was observed. The mixture of lowest protein content (1.1 g per 100 ml) was designed to mimic human milk. On this mixture the babies obtained about 2 g protein and 150 calories per kg body per day. Recovery was excellent, even though this protein intake was much lower than that often recommended for the treatment of kwashiorkor.

RESULTS

Creatinine Output

Urine was collected for 48-hour periods during the first weeks after admission to the hospital. Thereafter, when the balance studies had ended, 24-hour specimens were collected at intervals. Creatinine was measured by Folin's method.[10]

The course of creatinine excretion during recovery in two typical cases is shown in Figures 1 and 2. The 24-hour collections often had rather variable creatinine contents. For example, in one case for seven periods the outputs were 82, 64, 84, 112, 92, 86, and 90 mg creatinine per 24 hours, without any significant change in body weight. This is also shown by the fluctuations in the curve of Figure 1. It is therefore difficult to draw conclusions from a single specimen. We do not believe that this variability is caused simply by errors in urine collection, as great attention was paid to that point. Moreover, the fluctuations in total nitrogen output are smaller. Marples[19] has shown that in newborn infants the creatinine output is about 20 per cent higher on cow's milk than on breast-milk feeding. Many of our babies in the course of the balance studies were changed from one milk to another, but an alteration in either the type or amount of milk ingested could hardly explain the rapid day-to-day fluctuations. We have some evidence that they may be related to the urine volume; in one case, when antidiuretic hormone was given the creatinine output fell during the period of water retention and rose during the subsequent diuresis.

About half of the cases studied showed a more or less sharp rise in output during the first few days, followed by an abrupt fall, as in Figure 2. The cause of this effect is not clear; it seemed to be more marked in cases with edema than in the marasmic type of baby. The rise, however, often preceded the loss of edema. For the present purpose this transient rise has been ignored, since the other measurements to be correlated with creatinine excretion—body weight, skinfold thickness, and limb girth—cannot be made with validity until after the loss of edema. This usually occurred between 7 and 20 days after admission to the hospital, by which time

TABLE I

24-Hour Creatinine Output of Malnourished Babies at Different Stages of Recovery

Days after hospitalization	No. cases	Creatinine output	
		mg/day/cm ht	mg/day/kg wt
Under 20	19	0.79 ± 0.051[a]	9.4 ± 0.55
20–39	13	1.04 ± 0.056	11.9 ± 0.69
40–59	13	1.48 ± 0.120	14.3 ± 0.86
Over 60	8	1.86 ± 0.120	15.0 ± 0.60

[a] Mean ± S.E.M.

TABLE II

Increase in Body Weight, Creatinine Output, "Muscle Bulk" and "Fat Bulk" in Malnourished Infants During Treatment

Case No.	Days of treatment	Initial wt, % of standard[a]	Increase[b] in				Relative increase[c]		
			Weight A	Creatinine output B	Muscle bulk C	Fat bulk D	B/A	C/A	D/A
Kwashiorkor									
1	9	75	1.05	1.13	—	—	1.08	—	—
	65	75	1.22	—	—	1.55	—	—	1.27
2	25	62	1.18	1.33	—	—	1.12	—	—
	84	62	1.54	—	2.45	2.16	—	1.60	1.40
3	24	51	1.26	2.30	—	—	1.83	—	—
	49	51	1.34	—	1.55	1.64	—	1.16	1.23
11	43	69	1.18	2.43	—	—	2.06	—	—
	53	69	1.33	—	1.63	1.61	—	1.23	1.21
13	85	62	1.26	2.26	—	—	1.79	—	—
18	42	63	1.18	1.66	1.24	1.21	1.41	1.05	1.03
23	40	52	1.20	—	1.19	1.59	—	0.99	1.32
33	34	57	1.33	2.27	1.46	1.63	1.71	1.10	1.23
35	70	71	1.22	—	1.56	1.49	—	1.28	1.22
						MEAN	1.57	1.20	1.24
Marasmic kwashiorkor									
4	10	58	1.07	1.25	—	—	1.16	—	
	60	58	1.55	—	1.57	4.34	—	1.02	2.80
5	15	55	1.07	2.17	—	—	2.04	—	—
6	28	54	1.20	2.67	—	—	2.23	—	—
	84	54	1.53	—	1.79	2.89	—	1.17	1.86
7	35	39	1.56	2.20	—	—	1.41	—	—
8	62	52	1.53	3.30	—	—	2.15	—	—
15	20	44	1.27	2.62	1.40	1.80	2.06	1.11	1.43
16	48	42	1.52	2.08	2.30	2.60	1.38	1.51	1.71
19	42	45	1.37	1.50	1.20	2.36	1.09	0.88	1.72
20	87	57	1.50	1.72	—	—	1.15	—	—
21	65	52	1.44	—	1.90	2.38	—	1.33	1.65
26	28	31	1.51	1.95	1.62	2.55	1.29	1.07	1.69
27	56	58	1.54	1.90	2.36	3.93	1.24	1.53	2.55
28	56	47	1.59	1.87	2.20	4.60	1.17	1.38	2.88
29	50	59	1.33	1.77	1.82	2.47	1.34	1.37	1.86
30	90	42	1.95	2.50	4.60	5.51	1.28	2.36	2.83
32	57	48	1.73	2.94	2.70	6.00	1.71	1.57	3.45
34	84	42	1.74	2.13	2.57	4.71	1.22	1.47	2.70
						MEAN	1.49	1.37	2.24
Marasmus									
9	20	34	1.11	1.31	—	—	1.17	—	—
10	18	49	1.16	1.30	—	—	1.12	—	—
12	106	75	1.38	2.35	—	—	1.69	—	—
14	58	49	2.00	2.32	2.52	5.70	1.16	1.26	2.85
17	42	37	1.58	1.69	1.92	3.51	1.08	1.21	2.21
22	47	38	1.54	—	4.12	5.00	—	2.68	3.25
25	84	62	1.32	—	1.30	2.50	—	0.98	1.89
31	42	49	1.54	1.37	1.47	2.34	0.89	0.95	1.52
						MEAN	1.18	1.42	2.34
GRAND MEAN							1.45	1.33	1.95

Some cases have two entries because creatinine and somatometric measurements were made over different time intervals.

[a] Standard weights for age are taken from Nelson.[30]

[b] Calculated as ratio of final/initial value (see text).

[c] Ratio of increases to increase in body weight (see text).

creatinine output had fallen to a minimal level. This lowest level is designated the "initial creatinine excretion."

In order that comparisons can be made between babies of different ages and different sizes it is convenient, as Arroyave[14] has suggested, to relate the creatinine output to the height. A further advantage of this method of expression is that even in the malnourished baby the height changes relatively little over the period of treatment. The average creatinine output in relation to both height and weight at dif-

ferent periods of treatment is shown in Table I. The output per unit height is approximately doubled in two months of treatment. The output per unit weight also increases, although less dramatically. This, of course, is to be expected, since the children gain weight much more rapidly than they increase in height. The final value reached, 15 mg creatinine or 5.55 mg creatinine N per kg body weight per day, is in the range found by other workers for normal infants,[20,21] although a little lower than that of older children.[22]

If in each case the increase in creatinine output over the period of measurement is calculated as final/initial creatinine, and the increase in body weight as final/initial body weight, then the ratio *increase in creatinine : increase in body weight* gives the relative increase in creatinine output. This ratio was greater than unity in all but one case (Table II).

The ratio is rather variable from patient to patient. This is to be expected, since the increase in body weight involves changes not only in cellular tissue, but also in fat and water content, even though all measurements were made after the loss of edema. On the whole the ratio is lowest in the cases with the greatest initial weight deficit (Table III). These are the babies who have lost all superficial fat, and who present as marasmus or marasmic kwashiorkor. A ratio of 1.0 would indicate that during treatment fat and muscle are gained more or less uniformly. In the babies who were less severely underweight, the ratio *increase in creatinine output:increase in body weight* tends to be higher. In other words, the initial deficit in muscle mass is greater than the deficit in body weight. This fits in with the well-known clinical observation that a baby with kwashiorkor may, at a superficial glance, appear quite well nourished, the loss of muscle being masked by the presence of fat.[15] It would seem that such a baby may be two-thirds of its normal weight but contain only half the normal amount of muscle.

TABLE III

Increases in Creatinine Output, Muscle Bulk, and Fat Bulk During Treatment in Relation to Initial Body Weight

	Initial body weight	
	Less than 50% of standard[a]	More than 50% of standard[a]
Relative increase in creatinine (B/A, Table II)	1.29 ± .075[b]	1.55 ± .104
Relative increase in muscle bulk (C/A, Table II)	1.45 ± .152	1.22 ± .053
Relative increase in fat bulk (D/A, Table II)	2.35 ± .200	1.61 ± .135

[a] Standard weights in relation to age are taken from Nelson.[30]

[b] Mean ± S.E.M.

TABLE IV

Increase in Creatinine Output on Milk Feeds of Different Protein Content

Protein content of feed (g/100 ml)	No. cases	Increase in creatinine output (mg/cm/day × 100)
1.1	9	2.00 ± .25[a]
2.1	7	2.15 ± .34

[a] Mean ± S.E.M.

The protein content of the feed appeared to have little effect on the rate of deposition of muscle as measured by the rate at which creatinine output increased. Table IV shows the results obtained in cases that were kept on feeds of the same protein content (either 1.1 or 2.1 g per 100 ml) during all, or almost all, the period of observation. The increase in creatinine excretion did not differ significantly with the protein content of the feed.

Skin-fold Thickness and Limb Circumference

The measurements were made on the left arm and the right thigh of 25 babies, at intervals from the time of loss of edema. In 18 of the cases creatinine output was also measured; the groups on which the two sets of investigations were done therefore overlap but are not identical.

At the beginning of the study the length of the arm was measured from the tip of the acromion process to the lateral epicondyle of the humerus; half of this distance was taken and recorded. This fixed distance from the acromion process was taken as the site for all subsequent readings. Since the growing end of the bone is the distal end, this method should as far as possible ensure comparable readings. In the same way the thigh was measured from the an-

terior superior iliac spine to the medial epicondyle of the femur. Half this length was taken, and readings were made at this fixed distance from the medial epicondyle, since the growing end of the femur is the proximal end. Each limb was in normal anatomic position at the time of measurement.

At the standard site the circumference was measured with a steel tape fitting closely around the limb. Skin-fold readings were made with the Harpenden Skin-Fold Caliper Gauge;[23] in the arm they were taken at the standard level over the biceps and triceps muscles and also at the inferior angle of the left scapula. On the thigh they were made at the standard level on the medial, anterior, and lateral aspects. The caliper readings, on each occasion for each site, were repeated many times until there were at least three constant readings. The muscle thickness was obtained by calculating the radius of the cross-section of the limb and subtracting the skin-fold thickness; no allowance was made for bone in this simple calculation.

Typical curves of the changes in skin-fold and muscle thickness compared with body weight are shown in Figure 3. The skin-fold thickness followed the same general pattern at the different sites. The greatest increases were in the thigh and the triceps. In most cases the increase in muscle thickness was greater in the thigh than in the arm, but the patterns were the same. In cases where the investigations were carried out over exactly the same period, there was a correlation between increase in muscle thickness and increase in creatinine output (Fig. 4).

The limb measurements recorded in Figure 3 are linear, whereas body weight is a cubic quantity. In order to compare the increases, a rough calculation was made as follows: The cross-section of the limb was assumed to be a circle, whose circumference was known by measurement. The area of this circle was calculated, and from it were subtracted (1) the

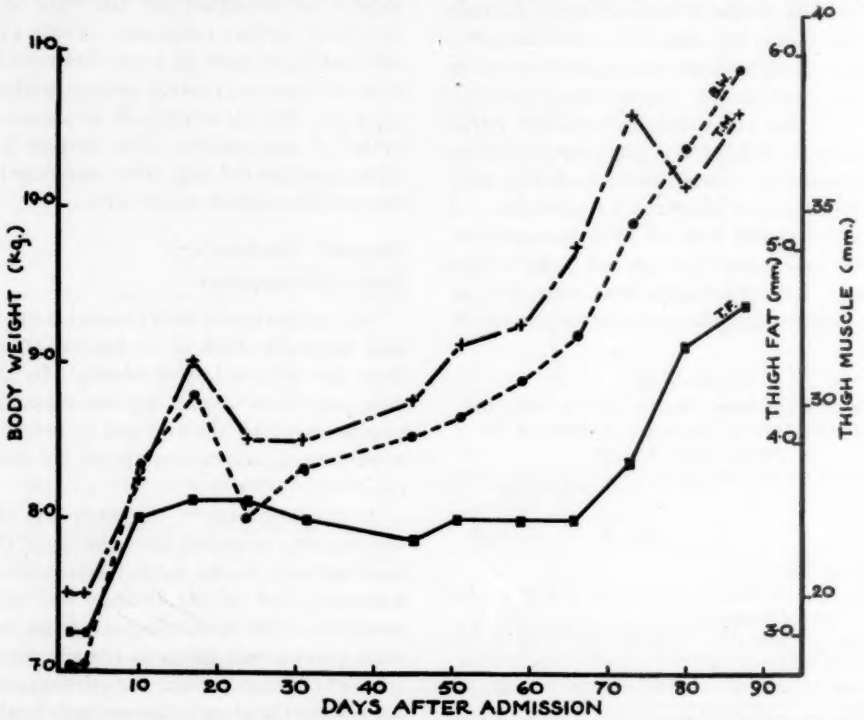

Fig. 3. Increase in body weight (● - - - - - ●), fat-fold thickness (■ ——— ■), and calculated muscle thickness (+ — - — +) in a malnourished infant during treatment. The figures for fat-fold and muscle thickness were calculated from measurements made on the thigh (see text).

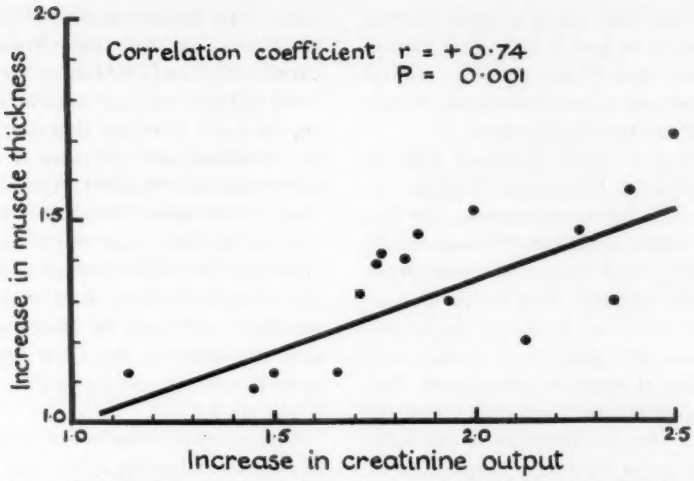

Fig. 4. Relation between increase in muscle thickness and increase in creatinine output in malnourished infants during treatment. The increase in each case was calculated as final/initial value.

area occupied by subcutaneous fat, calculated from circumference and skin-fold thickness, and (2) a correction for bone.

It was estimated from x-ray photographs that the average radius of the femur or humerus at the selected site in babies of this age group is about 5 mm. This estimate need not be accurate, as errors in it will have little effect on the final result. The residual area, after these subtractions, was taken to represent muscle. Since in the period of observation there is very little growth in length of the limb, these areas can be taken as estimates of bulk.

The increases over the period of investigation for both fat and muscle were calculated as final/initial volume, in the same way as for creatinine (see Table II). On the average the "muscle bulk" doubled, and the "fat bulk" increased by three times.

Calculations of this type are inevitably very rough, if only because the cross-section of the limb has been taken as a circle, which it certainly is not. On the whole the results confirm those of creatinine output. The increase of muscle was in most cases greater than the increase in body weight (see Table II, column C/A). The average for the ratio *increase in muscle bulk:increase in body weight* was 1.33, compared with 1.45 for the corresponding creatinine ratio. There was not, however, the same relation to the initial body weight. When the cases were divided into two groups according to the initial weight deficit, the relative increase in muscle was not significantly different in the two groups (Table III).

As might be expected, the relative increase in fat was much greater in the group with the greatest weight deficit, i.e. in those diagnosed as having marasmus or marasmic kwashiorkor.

DISCUSSION

Both the indicators—creatinine output and limb measurements—suggest that the decrease in muscle mass in these undernourished babies is greater than the body-weight deficit. At first sight it may seem strange that during recovery both muscle mass and fat should increase proportionately more than the body weight, since these two components make up a large part of the whole body.

The explanation lies in the fact that the undernourished baby, even after the loss of all clinically apparent edema, is not just a miniature of what it should be, i.e. a small baby of normal composition. In the first place, results obtained by Kerpel-Fronius[24] and in this laboratory[25] show that the water content of the body is still high, in the region of 75 per cent of the body weight, even after the loss of edema, at the time when the measurements described here

were begun. This high water content cannot be explained simply by loss of fat. If the water content is greater than 73 per cent, the normal proportion in fat-free tissue,[26] then the excess must be real and not merely apparent.

Secondly, there is much evidence that in malnutrition different tissues are depleted to different degrees.[27] Liver and muscle may lose more than half their substance,[28] whereas the supporting tissues, and organs such as brain and lungs, are less affected. For the purpose of discussion it is convenient to divide the organs and tissues into two groups, "mobile" and "fixed," although it must be recognized that there is no sharp distinction and such terms are purely relative. No information is available in the literature about the body composition of infants of the age of those in our cases, but according to the data quoted by Darrow and Hellersteiner,[29] in the adult the tissues that might be regarded as "mobile" contain some 60 per cent of body N, and the "fixed" tissues the remaining 40 per cent.

In Table V we have made a hypothetical "dissection" of a normal, a malnourished, and a treated infant of the same ages. According to this scheme, in an undernourished child of half the normal body weight, but without edema, the water content may be increased to over 70 per cent of the body weight; the fat content is reduced to less than one-third of the normal level. This fits in with the changes found in "fat bulk" during recovery. The "mobile" tissues, mainly muscle, may be reduced to one-third of the normal amount, and more than double during recovery. This fits in with the present results and with those of tissue analyses. The measurements of N/DNA in liver and muscle showed the following increases between initial and final biopsy: for liver, from 50 to 80 mg per mg;[8] for muscle, from 237 to 343 mg per mg.[10] It is true that the initial values are not doubled, but the ratio N/DNA certainly underestimates the real increase in protein content of the tissue, because it has been shown that in weanling rats recovering from protein depletion the DNA content of the tissues does not remain stationary, as in adults, but increases rapidly.[28] It must be emphasized, of course, that the data in this table are largely hypothetical and are put forward as a challenge for future work.

TABLE V

Postulated Body Composition of a Normal, a Malnourished, and a Treated Infant, Aged 1 Year

	Normal	Malnourished	Treated
Body weight (kg)	10.0	5.00	8.00
Fat (kg)	1.5	0.40	1.50
Water			
kg	6.2	3.75	4.75
% of body wt	62.0	75.00	60.00
% of fat-free wt	73.0	81.50	73.00
Nonfat solids			
Total (kg)	2.3	0.85	1.75
"Mobile" (kg)	1.4	0.45	1.10
"Fixed" (kg)	0.9	0.40	0.65

The practical conclusion is that, in such an infant, the reduction in the vital tissues is much greater than the reduction in body weight. The weight is therefore a poor guide to the degree of depletion.

Unfortunately, this conclusion at present is based only on the average results obtained in groups of cases. Because of the crudity of the methods the individual results are very variable. Moreover, the measurements described in this paper were made at repeated intervals, and the conclusions are based on changes rather than on absolute levels. Until the methods are refined, it seems to us optimistic to hope that such measurements, made once or repeated on one or two occasions, could give valid information about the degree of depletion in the individual case. To that extent, therefore, the original objective of this work has not been achieved.

SUMMARY

The 24-hour creatinine output was measured in malnourished infants at intervals after the loss of edema. After 2 months' treatment on milk diets the output more than doubled.

This increase in creatinine excretion was relatively greater than the increase in body weight over the same period. It is argued that, if creatinine output is a measure of muscle mass, the deficit in muscle mass at the time of admission to the hospital was considerably greater than the deficit in body weight.

Measurements were also made at intervals of limb circumference and skin-fold thickness. From these, estimates were calculated of "mus-

cle bulk" and "fat bulk." Over the period of observation both of these increased relatively more than the body weight. The fat increased most in the children who were initially most underweight.

It is concluded that in these malnourished babies, even in the absence of edema, the body-weight deficit underestimates the degree of protein depletion of the tissues.

The variability of the measurements is such that a single measurement cannot give a valid estimate of the degree of depletion in an individual case.

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Influence of Hunger on Sweetness Preferences and Taste Thresholds

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THE SENSE of taste and food preferences are undoubtedly influenced by body chemistry. However, little is known about the psychologic, physiologic, and chemical interactions which regulate the sense of taste and consequent qualitative and quantitative food selection. The first part of the present paper describes the relationship between hunger and sweetness preferences of 11,456 consumers. The second investigation involves the taste thresholds and sweetness preferences of a highly trained panel of eight judges under fasting and nonfasting conditions.

REVIEW

The "glucostatic" theory is frequently discussed in the literature. This theory concerns the controversial hypotheses of regulation of food intake based upon the fact that blood glucose concentrations rise and arteriovenous differences increase following ingestion of meals containing carbohydrates and proteins.[1] In tests on human subjects, Mayer[2] has found evidence for a relationship between blood glucose levels and hunger, appetite, or food intake. Albanese[3] has reported that approximately 30 g or 120 calories of sugar are needed to hurdle the postulated hunger threshold in the average 70-kg man. This investigator speculated that there might be a correlation between blood amino nitrogen and hunger and food intake, since fructose-containing sugars induced a greater blood amino nitrogen change than did comparable amounts of dextrose in fasting human subjects.[4]

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McCleary[5] associated osmotic pressure with specific hunger behavior, since preloading the stomachs of rats with glucose, fructose, urea, or sodium chloride resulted in depression of ingestion proportional to osmotic pressure.

According to Pfaffman and Bare,[6] salt deficiency did not alter the sensitivity of the taste receptors. Furthermore, enhanced sugar preference following the ingestion of insulin was not associated with a change in taste sensitivity.[7] Young[8] feels that food preferences definitely depend upon the diet, since protein-deficient rats preferred casein to sucrose, whereas rats on an adequate protein diet preferred sucrose.

Yensen[9] placed two human subjects on a low-salt diet and observed that during the periods of salt deficiency taste sensitivity for sodium chloride definitely increased, while sensitivity to sucrose, sulfuric acid, and quinine sulfate showed no change. In experiments with 70 human subjects, Siegel[10] concluded that there was a stronger relationship between hunger and palatability than between hunger and intake.

Olfactory acuity of human subjects has shown diurnal variations which are closely dependent upon food ingestion. Freely selected meals by human subjects were preceded by a period of increasing and followed by one of decreasing acuity.[11] These authors suggested that the precibal increase in olfactory acuity might be a measure of appetite intensity, whereas postcibal decrease in acuity might be a measure of satiety afforded by food ingested. Later work[12] verified their postulation; freely selected meals by 2 males and 14 females were preceded by a period of increasing and followed by one of decreasing acuity of the sense of taste for sucrose. Janowitz and Grossman,[13] however, reported only minor variations in acuity of the sense of

taste for sucrose and sodium chloride as well as the threshold for the odor of coffee, bearing no consistent relation to the presence or absence of hunger sensations and appetite. It should be mentioned that in the foregoing experiment there was but one test day for each subject.

The effects of withholding lunch and controlling the food intake at breakfast, on sucrose (gustatory) and isoamyl acetate (olfactory) thresholds have been reported by Furchtgott.[14] Gustatory thresholds were lower when no lunch was eaten than after lunch, whereas olfactory thresholds were not affected.

The accuracy of responses from professional tasters of alcoholic beverages was found to be highest during the half-hour before lunch and the half-hour immediately after lunch.[15] This investigator stated, " . . . although eating per se may dull the sensory receptiveness, other physical or psychological factors counteract this to the extent of making the period immediately after lunch better than most of the other times of day." In the foregoing case, accuracy increased with practice, then decreased due to fatigue.

Birch *et al.*[16] made the interesting observation that in rats the drive for food was not an increasing function of hours of deprivation, but that the function rose to a maximum at the accustomed time of feeding, then decreased with increased deprivation.

In an excellent review, Young[17] concluded that there were three complexly interrelated conditions which regulate food acceptance: conditions within the organism (appetite); conditions within the nutritive environment (palatability); conditions within the previous behavior of an organism (feeding habit).

METHODS AND MATERIALS

Consumer Study

The 1957 California State Fair, held in Sacramento from August 28 through September 8, was the location for interviewing 11,456 individuals. Several investigators have used the Fair population to determine sweetness preferences in wines, ice cream, and canned peaches with good reproducibility of results from year to year.[18–24]

Samples of Johnson cling peaches, varying in sucrose and/or total acidity (Table I) and packed under carefully controlled conditions in the pilot plant of the Food Technology Department, Davis, were evaluated.

TABLE I

Sucrose and Citric Acid Content of Canned Cling Peaches

Sample code	Soluble solids[a]	Total acidity[b]	pH
A	24.24	0.279	4.06
B	26.98	0.277	4.12
C	27.59	0.408	3.78
D	26.95	0.561	3.52
E	31.20	0.427	3.73
F	31.51	0.553	3.52
G	36.77	0.548	3.55

[a] Soluble solids of the pulped peaches plus syrup determined by refractometry and expressed as ° Brix.
[b] Expressed as per cent citric acid anhydride.

The peach-tasting booth, open to the general public from 10:30 A.M. to 8 P.M., consisted of 6 individual, partitioned windows through which samples were served. Children under 12 years of age were admitted if accompanied by an adult. Participants were met by a receptionist who recorded their sex, age, and frequency of consumption of canned peaches. Each consumer was given a score card and instructed to check the category which best described his state of hunger at that exact time.

1. ____I am extremely hungry
2. ____I am very hungry
3. ____I am moderately hungry
4. ____I am slightly hungry
5. ____I am not hungry at all

The above terminology was an adaptation of a scale described by Siegel.[10]

The participant then received two 4-oz samples of cold, diced peaches in cups coded "1" and "2" and was asked to check his preference. A "no preference" response was allowed. Care was taken to present the 21 possible paired comparisons an equal number of times; for each combination, the order of presentation was reversed in half the cases to compensate for any first-sample bias.

Laboratory Study

Four female and four male college students between 19 and 24 years of age were employed on a laboratory taste panel which met from 4:30 to 5:30 P.M. Monday through Thursday for 10 consecutive weeks. Good health, age, interest, and dependability were the only criteria used in selection of the panel.

All tests were designed so that four judges could serve the other four tasters who were seated in individual, partitioned booths equipped with constant lighting, temperature, and humidity. Upon completion of 5 to 10 minutes of tasting, the judges alternated sides, thereby reducing fatigue and monotony.

The first two weeks were spent in thoroughly acquainting the judges with the methods of tasting and training them to recognize small concentrations of sweetness, sourness, bitterness, and saltiness in aqueous solutions.

Thresholds for sucrose, sodium chloride, citric acid, and caffeine (reagent grades) were determined by the "choice method" of Richter and MacLean.[25] Subjects were presented with a labeled 100-ml beaker of tasteless, odorless, freshly distilled water to be compared against samples containing varying amounts of the compound being tested. Judges were allowed to sample the fluids in each beaker as often as they desired. Fountains in the booths provided for expectoration and only freshly distilled water was allowed for oral rinsing at the taster's discretion. Judges were instructed to indicate whether the paired solutions tasted identical or different and to identify the taste in terms of "sour, bitter, sweet, or salty." Solutions were presented at the rate of one per minute until two successive correct identifications were obtained. Servers introduced a distilled water blank (*Vexierversuche*) once or twice during a series. Tasters and servers were under constant supervision to assure uniformity of conditions. To eliminate guessing, fluids were kept in numerically coded containers and served in coded beakers, and series were randomized, i.e., same or different compounds could be submitted to each subject on any one day.

Original concentrations of the test compounds were as follows: Sucrose: 0.006, 0.012, 0.018, 0.024, 0.030, 0.036, 0.042, 0.048 M; citric acid: 0.0001, 0.0006, 0.0011, 0.0016, 0.0021, 0.0026, 0.0031, 0.0036 M; sodium chloride: 0.001, 0.007, 0.013, 0.020, 0.027, 0.034, 0.041, 0.048 M; caffeine: 0.0001, 0.0006, 0.0011, 0.0016, 0.0021, 0.0026, 0.0031, 0.0036 M.

As the judges' acuity increased with practice, the concentrations were adjusted accordingly until the final solutions were: Sucrose: 0.0008 to 0.022 M; citric acid: 0.000008 to 0.0002 M; sodium chloride: 0.0006 to 0.0300 M; caffeine: 0.00006 to 0.0008 M.

Each day, after all judges had completed the threshold series, apricot nectar varying in sweetness (8, 9, 10, 11, or 12 per cent sucrose) was tasted in paired sets and preference indicated. Since a "no preference" response was not permitted, judges were forced to make a choice. The 10 possible paired comparisons were presented an equal number of times in numerically coded 50-ml beakers.

TABLE II

Classification of Responses to Hunger

Classification	Degree of hunger (% of responses)					Total participation
	Extremely	Very	Moderately	Slightly	Not at all	
Sex						
Male	10.2	12.5	34.1	34.9	8.3	5,478
Female	6.1	11.1	32.2	38.4	12.2	5,978
Age						
Under 16	11.6	16.0	27.4	38.3	6.7	4,395
16–24	7.1	10.4	36.6	34.8	11.1	1,936
25–39	3.8	8.2	38.1	37.4	12.5	2,699
40–60	6.1	8.5	35.8	35.1	14.5	1,943
Over 60	11.8	11.2	32.5	32.5	12.0	483
TOTAL	8.1	11.7	33.1	36.7	10.4	11,456

TABLE III

Effect of Hunger on Peach Preference

Significant preferences only

Pair		Degree of hunger									
		Extremely		Very		Moderately		Slightly		Not at all	
1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
A	B	—	—	—	—	—	—	132[a]	88	—	—
A	C	—	—	—	—	—	—	—	—	—	—
A	D	—	—	—	—	—	—	—	—	—	—
A	E	—	—	—	—	—	—	—	—	—	—
A	F	—	—	—	—	92[c]	65	—	—	—	—
A	G	—	—	—	—	102[a]	63	136[b]	55	30[c]	16
B	C	—	—	20	46[a]	—	—	—	—	—	—
B	D	—	—	—	—	—	—	—	—	—	—
B	E	—	—	—	—	—	—	—	—	—	—
B	F	—	—	—	—	—	—	—	—	—	—
B	G	27[a]	10	54[b]	18	125[b]	44	146[b]	49	—	—
C	D	—	—	—	—	—	—	—	—	—	—
C	E	—	—	—	—	—	—	—	—	—	—
C	F	—	—	—	—	—	—	—	—	—	—
C	G	—	—	53[b]	17	126[b]	52	140[b]	68	41[c]	23
D	E	—	—	—	—	—	—	—	—	—	—
D	F	—	—	—	—	—	—	—	—	—	—
D	G	—	—	52[b]	19	138[b]	57	121[b]	59	32[c]	17
E	F	—	—	—	—	—	—	—	—	—	—
E	G	—	—	—	—	126[b]	47	139[b]	70	39[b]	14
F	G	—	—	—	—	137[b]	44	134[b]	63	—	—

[a] Significant at 1% level of probability. [b] Significant at 0.1% level of probability. [c] Significant at 5% level of probability.

The experimental conditions of fasting were not initiated until each judge had ceased to improve in acuity with practice. At this time, a schedule was effected in which the students consumed their usual meals in the dormitory dining facilities except that on alternate days no food or liquid (except water) was allowed between breakfast and the test hour (4:30 P.M.). A check of their normal eating habits showed that all subjects were accustomed to a moderate, fairly standardized breakfast (eggs, juice, toast, milk, coffee) and a light lunch (sandwich, salad, fruit, milk). Subjects attended classes and participated in extracurricular activities as usual during the 10-week experiment.

RESULTS AND DISCUSSION

Consumer Survey

Classification of the peach tasters (Table II) showed that more females than males participated and that a slightly different pattern of response was evident between the sexes. Fewer females than males were "extremely hungry," whereas fewer males than females were "not hungry." Consumers under 16 and those over 60 gave the most frequent "extremely hungry" responses. Regardless of age or sex, the majority of the population sampled was slightly to moderately hungry prior to sampling the fruit.

Table III summarizes the peach preferences with values presented only for the significant combinations. It is immediately apparent that sample G, which was extremely sweet and highly acidified, was inferior to all other samples. Only one significant preference was obtained from the extremely hungry tasters, suggesting that extreme hunger decreases discrimination. One could speculate also that individuals who were not hungry at all might tend to have no preference, since neither sample would appeal to them. The data showed that 6.9 per cent of the "not hungry" group and 7.5 per cent of the "extremely hungry" group indicated no preferences, whereas "very," "moderately," and "slightly hungry" consumers gave no preference answers in 5.0,

TABLE IV

Hunger and Sweetness Preference in Apricot Nectar[a]

Classification and sex	Sample and % sucrose A 8.0	B 9.0	C 10.0	D 11.0	E 12.0	No. paired comparisons
Not Fasting						
Males	8	18	25	33	44	
Females	16	15	26	36	35	
TOTAL	24	33	51	69	79	256
Fasting						
Males	10	18	28	37	35	
Females	10	24	22	30	34	
TOTAL	20	42	50	67	69	248

[a] Values represent total comparative preferences for paired samples.

3.7, and 4.6 per cent of the total responses, respectively. The over-all preference was little if at all affected by hunger. If a quantitative measure of the peaches consumed could have been recorded, the results would undoubtedly have differed from the qualitative responses collected.

Laboratory Panel

Apricot Nectar Preferences: Hunger had little effect on total comparative preferences for sweetness in apricot nectar (Table IV). To determine whether fasting affected individual panel members, the frequency with which tasters preferred sweeter samples, regardless of sugar increment, was determined (Table V). Although judges differed from each other in their responses, only one subject (S.M.) demon-

TABLE V

Individual Responses to Sweetness in Apricot Nectar

Sex and subject	Preference for sweeter sample[a] Not fasting (%)	Fasting (%)
Males		
W. M.	71.9	81.3
K. S.	75.0	68.8
R. T.	96.9	93.8
K. Z.	75.0	75.0
AVERAGE	79.7	79.7
Females		
S. M.	40.6	59.4
J. C.	87.5	87.5
A. R.	84.4	75.0
C. W.	81.3	78.1
AVERAGE	73.4	75.0
GRAND AVERAGE	76.6	77.4

[a] Individual percentages represent 32 separate paired evaluations.

TABLE VI

Effect of Training on Taste Thresholds

Comparison of first and sixth determination

Subject	Sucrose 1st	Sucrose 6th	Citric 1st	Citric 6th	NaCl 1st	NaCl 6th	Caffeine 1st	Caffeine 6th
	MOLARITY							
Males								
W. M.	0.036	0.022	0.00160	0.00010	0.034	0.030	0.00160	0.00020
K. S.	0.024	0.008	0.00060	0.00004	0.013	0.003	0.00060	0.00008
R. T.	0.036	0.008	0.00210	0.00001	0.034	0.005	0.00160	0.00040
K. Z.	0.018	0.010	0.00110	0.00010	0.020	0.003	0.00110	0.00060
Females								
S. M.	0.012	0.006	0.00060	0.00001	0.020	0.007	0.00060	0.00040
J. C.	0.018	0.002	0.00010	0.00003	0.020	0.005	0.00110	0.00030
A. R.	0.018	0.006	0.00210	0.00004	0.007	0.003	0.00310	0.00060
C. W.	0.018	0.004	0.00110	0.00003	0.020	0.009	0.00160	0.00060
GROUP AVERAGE	0.022	0.008	0.00116	0.00005	0.021	0.008	0.00141	0.00040

TABLE VII

Individual Identification Thresholds

Sex and subject	Sucrose		NaCl		Citric acid		Caffeine	
	Not fasting	Fasting	Not fasting	Fasting[a]	Not fasting	Fasting	Not fasting	Fasting
	MOLARITY $\times 10^{-4}$							
Male								
W. M.	40	160	110	100	0.6	0.2	5.0	5.0
K. S.	60	40	40	50	0.3	0.1	0.7	3.0
R. T.	90	50	60	7	0.3	0.2	1.9	1.0
K. Z.	70	80	70	60	0.4	0.1	6.0	8.0
AVERAGE	70	81	62	57	0.4	0.2	4.2	4.2
Female								
S. M.	40	50	70	10	0.3	0.2	2.3	4.0
J. C.	9	9	20	50	0.2	0.2	2.4	0.8
A. R.	60	70	30	30	0.2	0.6	6.0	4.0
C. W.	90	20	50	30	0.1	0.2	4.0	1.9
AVERAGE	46	37	34	21	0.2	0.3	3.7	2.5
GRAND AVERAGE	60	60	50	40	0.3	0.2	4.0	3.0

[a] Significant difference between male and female responses to NaCl at the 5% level of probability.

strated an increase in preference for the sweeter sample with hunger. In general, regardless of method of classification, hunger did not affect sweetness preferences.

Taste Thresholds: Blakeslee's statement, "Different people live in different worlds so far as their sensory reactions are concerned,"[26] is well-demonstrated in Table VI. Four important conclusions can be derived from these data: (a) wide variation between individuals; (b) decided decrease in all thresholds with practice; (c) wide variation between individuals in degree of improvement with practice; (d) much lower original as well as final thresholds shown by females as a group than by males.

Threshold values reported for determination 1 are within the range of thresholds reported in the literature. Knowles and Johnson[27] published values of 0.003 M, 0.0224 M, and 0.05 M for low, medium, and high sucrose thresholds, respectively. For citric acid, Fabian and Blum[28] list a value of 0.0007 M. According to Richter and Campbell,[29] humans first recognize the taste of sodium chloride in solution at 0.065 per cent (0.011 M). Threshold values for caffeine have been observed at 0.0002 M to 0.0032 M.[13] With the exception of the caffeine thresholds, training subjects resulted in lower final thresholds than the literature values reported above.

TABLE VIII

Hunger and Taste Thresholds

Compound and condition	No. judgments	Average difference threshold	Average identification threshold
		MOLARITY $\times 10^{-4}$	
Sucrose			
Not fasting	18	50	60
Fasting	16	30	60
NaCl			
Not fasting	18	30	50
Fasting	16	20	40
Citric acid			
Not fasting	16	0.3	0.3
Fasting	15	0.2	0.2
Caffeine			
Not fasting	16	3.0	4.0
Fasting	15	3.0	3.0

Since there were only minor fluctuations in thresholds after the sixth set of determinations, the fasting vs. nonfasting experiment commenced with the eighth determination to give the results shown in Table VII. Average panel values showed no variation as a result of fasting, thereby agreeing with results obtained by Janowitz and Grossman.[13] Females seemed to be slightly more sensitive to the compounds when they were hungry than were males. Only one subject (R.T.) was consistently more sensitive to all compounds when fasting. It is of interest that the only statistically different values ob-

tained were between male and female responses to sodium chloride.

A comparison between the average difference thresholds and the average identification thresholds is made in Table VIII. There is a slight, but not significant, trend for lower thresholds under fasting conditions. Except for citric acid, a difference was established between plain water and the compound in solution before the correct identification could be made.

SUMMARY

No relationship was observed between degree of hunger and sweetness preferences in canned cling peaches as evaluated by 11,456 consumers under uncontrolled conditions. Similar results were obtained from a highly trained laboratory panel of eight judges tasting sweetened apricot nectar. In addition, fasting vs. nonfasting conditions had no pronounced effect on difference thresholds nor upon identification thresholds for sucrose, citric acid, sodium chloride, or caffeine. Taste thresholds for all four compounds were significantly reduced with training. Female judges, as a group, were more sensitive than were the males.

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Tell me what you eat, and I will tell you what you are.
—A. BRILLAT-SAVARIN

Test of the Psychogenic Theory of Obesity for a Sample of Rural Girls

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RESEARCH on the etiology of obesity has indicated the multifactor nature of this phenomenon. The energy ingestion-expenditure balance, glandular disturbances, constitutional development arising from genetic factors, and psychogenic bases of obesity have been identified.[1-3] Bruch has done much to bring attention to the psychogenic theory for childhood obesity.[4-9] According to the psychogenic theory,[10-13] obesity in children may be regarded as a symptom of disturbing interpersonal relations, which are generally family centered. The purpose of this paper is to present some data to test the psychogenic theory of obesity for a sample of rural Iowa girls.

THE PSYCHOGENIC THEORY OF OBESITY

Bruch found that obesity among children occurs within a family system which displays a fairly uniform set of psychopathologic characteristics.[6-8] Obese children frequently are only children, or if there are other children, they are apt to be the youngest children. Families are small. The mother generally is oversolicitous and protective toward her child, but these manifest attitudes and behavior patterns are believed to be compensations for her hostility toward and rejection of her child. Feeding her infant and later her growing child provides the mother with a continuous method of demonstrating her protectiveness toward her child. At the same time, compensation for the mother's rejection or hostility toward the child is shown in her restriction of the child's social contacts and limitations of his physical activities. Under such conditions, obesity becomes the natural result of overindulgence in food and reduced physical activity.‡

Bruch's theory is based upon extensive interviews with parents of obese children and observation of the children.[6] Specifically, her sample for detailed study included 40 obese children. The parents of these children were predominantly recent immigrants in a marginal economic position. Highly disharmonious marital relations appeared to be more customary than exceptional for the parents of the children. While her data obviously came from a very restricted population, the "family frame" for obese children derived from observation of these families has gained wide currency.

Implicit in the summarization of Bruch's theory is a psychoanalytic interpretation of the etiology and meaning of obesity in children or adults. A basic premise of the psychoanalytic theory is the assumption that obesity is associated with eating and gaining of satisfaction during the oral state. When the ego is unable to find gratification in normal re-

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‡ Iverson *et al.* have summarized the position taken by Bruch in regard to family characteristics of obese children.[24] Bruch's recent publication[9] summarizes current views on the psychologic aspects of obesity. While Bruch emphasizes this it is incorrect to refer to obesity "as if it were a disease entity" and that "it is more correct to speak of different types of obesities,"[9] the bulk of her presentation follows the psychogenic theory of obesity in the context of a defense mechanism resulting from severe emotional or personality disturbances.

lationships, regression to earlier, satisfying forms of behavior occurs. The unconscious association between eating and overcoming frustration reflects the individual's desire to regain the security of the relationship with his mother during his oral stage of psychosexual development. Ingestion of food is a means of re-establishing the once-existing unity between the child and his mother. Obesity thus becomes the "oral ego's" attempt to resolve the depressive situation arising from disturbances in interpersonal relationships.[11]

Additional psychoanalytic interpretations have been cited. These included the symbolic meaning of large body size,[4,6,8] rejection of femininity or denial of the oedipal rivalry with the mother,[14] unconscious identification with the father,[3,14] or masochistic self-punishment for incestuous and exhibitionistic wishes.[14,15] In all cases, obesity is regarded not only as "an autistic symbol at a deep level of oral regression but a symptom representing an autoplastic method of tension discharge to the point of distorting the shape of one's own body in order to symbolically satisfy unconscious motivations."[11]

HYPOTHESES

If the elements of the psychogenic theory of obesity are generally valid, the following hypotheses should hold true:

1. The family characteristics of the obese girls will be different from those of the nonobese girls; i.e., size, sibling position, and social status.

2. Obese girls will show greater indications of personality disturbances than nonobese girls.

3. Obese girls will do less well scholastically than nonobese girls. This hypothesis follows from the second hypothesis and from the assumed precarious emotional relationships which the obese girls have with their mothers.

4. Obese girls will be less active physically than nonobese girls.

5. Obese girls will have less highly developed sex-role identifications than nonobese girls. This should follow from the view that obesity is a symptom of withdrawal from a hostile world. If the degree of sex-role identification is taken as an index of present or intended future participation in the world of interpersonal relationships, sex-role identification as measured by use of feminine sex symbols or reported interest in boys should provide a test of this hypothesis.

SAMPLE AND METHODOLOGY

The present data were obtained from 111 girls who attended four rural consolidated schools in a central Iowa county. Their ages ranged from 10 to 16 years; the mean age and the median age for the group was 12.2 years. These girls were voluntary participants in a project dealing with nutritional needs of children conducted by the Iowa Agricultural and Home Economics Experiment Station. The psychometric data were gathered as part of this project during April and May, 1956. Home interviews with the girls and their mothers during the summer and fall of 1956 were used to obtain family background data and the responses of the girls to several attitude questionnaires.

Physique classification was determined on the basis of measurements taken in the spring of 1956 at about the time of obtaining the psychologic data. The girls were classified into three physique groups—heavy and obese, medium, and thin—by means of the Wetzel grid channels.* A total of 183 girls were still participating in the nutrition project during the spring of 1956, but data are reported for only the 111 girls who remained in the same one of the three channels defined above during the preceding three-year period for which measurements were available. Ranges and mean percentages of over- or underweight for girls classified into the three Wetzel grid channels used in the study are shown in Table I.

Psychologic tests administered to the girls were the Otis Mental Abilities Test, short form, Beta and Gamma;[16] the Jastak-Bijou Wide Range Achievement Test;[17] and the

* The girls classified as A_3 or A_4 were considered as heavy and obese. The medium physique group represented the A_2, A_1, M, and B, classifications. The B_2, B_3, and B, groups were combined to become the thin physique group for this study; see Wetzel.[25]

TABLE I

Percentage of Weight Deviation from Weights in Baldwin-Wood Tables for Girls of Specified Age and Height

Physique classification	No. girls	Range (%)	Mean (%)
Heavy and obese	21	20 to 67	39.1
Medium	68	−10 to 19	3.5
Thin	21	− 5 to −28	−14.0

Mental Health Analysis.[18] Physical activity data were obtained by means of four one-day activity records kept by the girls. The questionnaires regarding the girls' sex-role identification are described later.

FINDINGS

Family Variables

None of the variables used to describe characteristics of the girls' families differentiated significantly among the three groups of girls when the chi-square or the median test was used to test the significance of the differences among various observations. Place of residence, defined as farm and nonfarm, was unrelated to the physique classification. Sizes of families ranged from 1 child to 14 children, but when the median number of children in the families of girls in each physique group were compared, no significant difference was found. "Only children" were not represented beyond the level of chance in any of the three groups. Ordinal position in the family, defined as oldest, middle, or youngest, was independent of the physique classification.

The occupation of the father, whether or not the mother was employed outside the home, the education of the parents, and a home index score were used as separate estimates of the socioeconomic status of the families.* There were no significant differences for any of the analyses based upon different measures of family social status for the three physique groups.

* A slightly modified form of the index reported by Gough[26] was used to measure the material and cultural levels of the homes. Possession of two material items, a television set and a deep-freezer, were added to the scale reported by Gough.

Psychologic Test Score Comparisons

When the responses of the girls to the psychologic tests were classified by the three physique groups and means were computed, the results shown in Table II were found.

Mean achievement scores for the girls in the three physique groups could not be directly compared, since the three groups were not matched by age. For this reason, the measured achievement scores were corrected for the varying ages and class levels of the girls by subtracting the girls' autumn grade levels from their measured achievement scores. After achievement scores were transformed in this manner, means were determined for the three groups of girls. Nonsignificant results were obtained for each of the three sets of corrected achievement scores, although the heavy and obese girls had a significantly higher mean intelligence score than the other two groups of girls.

Two major subscores, mental health assets and mental health liabilities, and a total score may be derived from the Mental Health Analysis test. Means for mental health asset scores were not significantly different from one another, although significant differences at the 0.05 level were found for the liabilities subscore and for the total score. It was predicted that the heavy and obese girls would display the greatest indications of personality disturbance, but this was not the case.

Means for the heavy and obese and medium girls were fairly similar, and both were considerably lower than the means observed for the girls in the thin classification. As judged by the means, the girls in the thin group reported fewer personality disturbances.

Physical Activity

The data from the four one-day records provided by the girls were coded in terms of hours of sleep and hours of mild, moderate, and vigorous activity per day. Mean activity levels for the three groups of girls are shown in Table III.

The striking feature of the mean activity levels is the remarkable uniformity for each set of means. No statistical tests were per-

TABLE II

Psychologic Test Means

Physique groups	No. girls	Otis intelligence score	Achievement minus grade level			Mental health scores		Total score
			Reading	Spelling	Arithmetic	Assets	Liabilities	
Heavy and obese	21	110.0	1.88	0.04	1.34	78.2	65.6	143.8
Medium	69	105.3	0.93	0.00	0.98	76.0	64.3	140.3
Thin	21	105.0	1.28	0.02	1.36	83.0	75.7	158.7
Probability level[a]		<0.001	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05

[a] Based on Kruskal-Wallis tests. See Siegel.[23]

TABLE III

Mean Hours Per Day Spent in Specified Levels of Activity

Physique group	No. girls	Sleep (hrs)	Activity (hrs)		
			Mild	Moderate	Vigorous
Heavy and obese	21	9.5	9.9	3.5	1.0
Medium	69	9.6	10.1	3.3	1.0
Thin	21	9.9	10.1	3.1	1.1

formed because of the near identity of the means.

Sex-role Identification

Sex-role identification was defined in two ways: (1) use of appearance symbols associated with the female sex in our society and (2) interest in boys. The content of each scale and its statistical properties have been reported elsewhere.[19] High scores for either scale indicate greater use of symbols or greater heterosexual orientation.

Since age was not controlled among the three groups of girls, direct comparisons of scores on the two sex-role identification scales could not be made. However, it was possible to match 13 girls in each of the three physique groups by age within a half year. Means for the two sex-role identification scores for the three age-matched groups are listed in Table IV. Nonsignificant results were found in each case.

TABLE IV

Sex-Role Identification Mean Scores for Age-Matched Girls

Physique groups	No. girls[a]	Use of sex-role symbols	Interest in boys
Heavy and obese	13	28.0	29.7
Medium	13	27.5	28.4
Thin	13	23.8	29.5
Probability level[b]		0.20< P <0.30	0.95<P <0.98

[a] Matched by age to one-half year.
[b] Based on the Kruskal-Wallis test.

Weight of Parents

A age-height-weight classification of parents was also tested for association with the physique classification of the girls. Usable data were available for only 105 fathers and 108 mothers. An average or normal weight range for the parents was established by calculation of the specified weights for given ages and heights plus or minus 10 per cent.[20] An overweight person was defined as one whose weight exceeded the upper 10 per cent limit; an underweight person was one whose weight was less than the lower 10 per cent limit. Only 4 fathers and 11 mothers were underweight by these standards. These cases were deleted

TABLE V

Cross-Classification of the Girls' Physique Group by Weight Classification of Fathers and Mothers

Physique groups of girls	Fathers				Mothers			
	Overweight		Normal-weight		Overweight		Normal-weight	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Heavy and obese	10	6.5	6	9.5	12	7.0	6	11.0
Medium	26	26.0	38	38.0	22	23.3	38	36.7
Thin	5	8.5	16	12.5	4	7.8	16	12.2
	$\chi^2 = 5.60$; $0.05 < P < 0.10$				$\chi = 9.00$; $P < 0.02$			

from the chi-square analyses because the expected frequencies would be too small. The weight cross-classifications for the remaining groups are reported in Table V.

The observed number of heavy and obese girls who had overweight parents exceeded the expected number, while girls in this group who had normal weight parents were underrepresented. Medium girls who had overweight and normal-weight parents were proportionally represented in each category. The number of thin girls actually having overweight parents was lower; those having parents of normal weight was higher than expected. The comparison based upon data for mothers was clearly significant ($P < 0.02$) while the comparison based upon data for fathers approached significance ($0.05 < P < 0.10$).

DISCUSSION

The present data failed to offer any support for the psychogenic theory of obesity for the present sample of girls. None of the family variables that were tested revealed any significant difference between characteristics of families of the obese and nonobese girls. The obese girls displayed no apparent retardation in their scholastic achievement, although this might have been the expected result if their obesity was related to psychologic disturbances. The most critical test of the psychogenic theory of obesity that could be made with the present data rested upon the analyses of the mental health scores. In these analyses the means for the obese girls were very similar to the means for the medium physique group. Contrary to the finding of Johnson, Burke, and Mayer,[21] the obese girls did not appear to be less active physically than the nonobese girls. In addition, the obese girls displayed no tendency to be retarded in their sex-role development in comparison with the other two groups of girls. The data indicated that the three groups of girls were highly homogeneous in all but one of the variables tested.

The one variable which differentiated the three groups of girls was the weight classification of their parents. Although a small sample of heavy and obese girls was used in this study, the validity of this result is enhanced because of the stability of the major dependent variable. Only girls who had remained in the same major Wetzel grid channels for at least three years were included in each of the three physique groups.

Similar results have been reported by Tolstrup.[22] He compared 40 obese children with a control sample of nonobese children. When he tested the elements of the psychogenic theory of obesity, he found that adiposity in his sample of children did not conform to any "uniform pathological picture from a psychogenic point of view."[22] Instead Tolstrup concluded that the etiology for most of his cases was founded on faulty eating habits for his sample of Danish children.

We do not claim that a crucial test of the psychogenic theory of obesity has been accomplished. The heavy and obese girls in the present sample were probably not as obese as the children Bruch studied or the children frequently cited in the psychoanalytic literature, but they had been heavy or obese for at least three years prior to the time for which present measurements are reported. Although Bruch did not indicate how the overweight figures were determined, she divided her sample into three ranges of overweight—moderate, between 25 and 39 per cent; severe, between 40 and 69 per cent; and extreme, between 70 and 120 per cent overweight.[6] For her sample, 27.5 per cent of the children were moderately overweight, 52.5 per cent severely, and 20 per cent were extremely overweight. When Baldwin-Wood norms were used for the present sample of 21 heavy and obese children, one girl (4.8 per cent) was below the 25 per cent limit used by Bruch for moderately overweight, 52.4 per cent were moderately overweight, and 42.8 were severely overweight. None of the girls was extremely overweight by Bruch's percentage criterion, but it should be reiterated that the Baldwin-Wood derived percentages for the present data may or may not be similar to Bruch's percentages.

In addition to the definition of obesity, the question may arise of whether the present study is valid as a test of the psychogenic

theory of obesity.* With less than a complete psychoanalysis of the subjects the answer is "no", but by the criterion that the data utilized are at least grossly related to relevant characteristics predicted from the theory the answer is "yes". Only one set of data directly pertained to personality characteristics of the girls. However, these data were derived from a self-administered pencil-and-paper test which suffers from all the weaknesses of such personality tests. When the results from all the tests of differences among the family, psychologic, social, physical activity, and attitude data are taken jointly, the conclusion appears clear: The psychogenic theory of obesity must be rejected for the present sample of overweight rural girls.† It is possible that different results would emerge if more "severely" and "extremely" overweight girls were tested in comparison with nonobese children.

This does not mean that such a theory is without merit. In the extremely disturbed family situations which come before psychiatrists and social workers, the theory may be a valid guide for most cases.[9] The present sample of girls came from rural homes where it is assumed that most family relationships are within reasonable limits of security and frustration. The question then becomes one similar to that tested by Tolstrup: What proportion of the cases of obesity can be explained by the psychogenic interpretation; or, to what population of cases should the theory be limited? This is not an idle academic question, for obviously different therapeutic processes follow depending on the interpretation of causal factors.

The results of the present investigation, based on the hypotheses mentioned, suggest strongly that in this study factors other than psychologic relationships within the family must be considered. Obesity may indicate several things: it may be psychogenic; it may be generated by constitutional factors; it may be begun and established by faulty eating habits; or it may be the result of the interaction of some combination of these and other factors.

Too frequently, however, psychogenic stigmata are attached to cases of obesity. Concern for alleged abnormality among heavy and obese children may help create problems in some cases. The present findings indicate that the unqualified acceptance of the psychogenic theory of obesity has virtually no explanatory value for the present sample of overweight rural girls. Since the present sample was not randomly chosen from a defined population of rural children, generalization to a larger population involves making several assumptions about the character of the sample. If the present sample is "representative," then generalizations of the psychogenic character of obesity for rural girls are severely questioned by the present data. Possible extension of the findings to boys and to the urban population of children must await further research.

SUMMARY

Data from rural Iowa girls aged 10 through 16 were organized to test the psychogenic theory of obesity. The girls were classified by means of the Wetzel-grid method as heavy and obese, medium, or thin. Only girls who remained within the same major channels for three years were used as subjects for this study. Comparisons among family-structure variables, intelligence scores, spelling, arithmetic and reading achievement scores, mental health analysis scores, levels of physical ac-

* For a criticism of the attempts to test psychoanalytic concepts and hypotheses empirically in family research, see Simpson.[27]

† Data are also available for 27 of the heavy and obese girls and a control sample of 27 girls of the medium-physique group. They were selected on the basis of physical measurements taken during the 1953–1954 school year, but the two groups included only girls who remained in the same groupings for the subsequent three years. Girls were matched by height within 1 inch and by age within 6 months. These two groups of girls failed to show any significant differences in levels of physical activity, intelligence, achievement, or mental health analysis scores. Various family characteristics that were tested also failed to disclose any factors which differentiated between the two matched groups. These data based upon comparisons of individually matched heavy and obese and medium-physique girls confirm the results obtained with the larger group of 111 girls; see Pickenpaugh.[28]

tivity, and sex-role identification scores were made for the three groups of girls to test several hypotheses derived from the psychogenic theory of obesity. None of the tests supported the psychogenic theory of obesity.

However, it was found that the heavy and obese girls tended to have overweight parents more frequently than would have been expected. This finding suggested that constitutional factors or family eating habits may be involved in the children's obesity.

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Course and Treatment of Obesity*

M. V. Egorov, L. M. Levitskii, and K. M. Prostiakov

The problem of disturbances in fat metabolism is acquiring an ever greater importance in the contemporary study of the symptoms and course of internal diseases. Primarily, disturbances in the regulation of fat and carbohydrate metabolism form the pathogenetic basis for such widespread diseases as atherosclerosis, obesity, and various lipodystrophies of individual organs and systems. However, the course and especially the treatment of these disturbances of fat metabolism still need further study.

Editorial note: In 1956 the National Institutes of Health of the Department of Health, Education, and Welfare established a Russian Scientific Translation Program. The objective is to acquaint the American scientist with Russian medical-biologic research.

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FACTORS IN THE PATHOGENESIS OF OBESITY

Most evident and pronounced are disturbances of fat metabolism in obesity. Taking into account the present considerable incidence of this ailment, as well as the lack of experience on the part of general practitioners in methods of treating it, the Clinic of Medical Nutrition of the Institute of Nutrition, Academy of Medical Sciences, USSR, has been working for the last three years on improving diet therapy in obesity and has also been studying the problems of its clinical manifestations and pathogenesis.

The observations compiled by the Clinic, which cover over 450 cases, permit an approach to a classification of obesity, a study of its pathogenesis and, on the basis of this, to the problems of treatment.

Neuroendocrine Disturbances

Multiple mechanisms of the central nervous system participate in the regulation of fat metabolism—those of the cortex and subcortical areas, and primarily the pars intermedia of the pituitary and the diencephalon. The autonomic nervous system, the spinal cord, and the peripheral nervous system are also of vast importance. Numerous pathologic processes, both of organic and functional origin, are capable of upsetting this complex regulatory system and may lead to the development of excessive deposit of fat. These disturbances in obese patients may be linked with changes in the cortical activity of the central nervous system.

Levitskii and associates,[1] in a study of conditioned motor reflexes mediated through a secondary signal system, noted disturbances in the circuit-closing function of the cerebral cortex, sluggish function of the processes of excitation, as well as pronounced inertia of the main nerve processes in the majority of patients.

* Original title: Klinika i lechenie ozhireniia.

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A limited number of tearsheets of this article will be available from the National Institutes of Health, Russian Scientific Translation Program, Bethesda, Md.

Prostiakov[2] has studied in obese patients the complex of nerve centers having "multilevel" cortico-subcortical distribution (the alimentary nerve center). Overexcitation of the alimentary nerve center was observed in many patients. Together with the processes of overexcitation there was also a reduction of its inhibitory function.

Disturbances of neuroendocrine function in obese patients have been quite inadequately reflected in current literature. In our observations disturbances of the autonomic nervous system have been determined by widely adopted clinical tests, the adrenal-histamine test among them. According to these data, in obese patients a hypervagotonic reaction clearly prevailed, and was also often accompanied by hyposympatheticotonus. Besides these dissociated reactions, reactions of an amphotonic type were observed more rarely. Thus, the disturbances of the nervous system that are observed in obese patients are multiform.

It is essential to note that the unique character of these disturbances is in a certain measure connected with the form of obesity. In the metabolic-alimentary forms, phenomena of heightened excitability of the alimentary nerve center and depression of the processes of its inhibition predominate; in the cerebroendocrine forms, disease of the diencephalon—of the hypothalamus and the pars intermedia of the pituitary, in particular—is more pronounced.

However, it would be erroneous to ascribe the entire problem of obesity to disturbance of the nervous system.

Endocrine-Metabolic Disturbances

The endocrine-humoral link plays a subordinate but important role, and the nature of the disturbances that arise is unique and has a rather broad range of effects. From the point of view of contemporary science it is incorrect to think of an isolated functional disturbance of any one endocrine gland. One characteristic of these polyendocrine disturbances is the presence of dissociated shifts: for example, the function of one gland may be accelerated, that of another slackened.

An important feature of the endocrine-metabolic disturbances in patients with obesity is their unique character, which is determined by the range of normal (maximal or minimal) functional potentialities remaining in one or another endocrine gland. Thus, it is correct to characterize these disturbances as alterations of the functional activity of the glands. It is not yet a pathologic endocrine function, but endocrine-metabolic shifts predicated on the altered interrelations of the central regulatory apparatus.

For characterization of these disturbances the composite data of investigations into the insular apparatus (islands of Langerhans)[3] and the thyroid gland[4] in patients with obesity may be cited. Presented in Table I are the data on changes in the functional activity of the insular apparatus and of the thyroid gland, the percentage of demonstrated deviations from the normal of biochemical studies and clinical tests having been taken into account.

These composite, antagonistically oriented disturbances of the functional activity of the insular apparatus and thyroid gland (one with plus, the other with minus activity) may result in the increased deposit of glycogen and increased fat formation, as well as in the reduction of fat mobilization. It should be noted, however, that, according to recent data, the presence of hyperinsular reaction in obesity may have a more complex origin: initially, there is increased formation and deposit of glycogen, and only secondarily does insulin secretion occur.

Defective endocrine-metabolic relationships are not exhausted with the functional disturbances of the pancreas and the thyroid gland. The pathogenetic endocrine-metabolic form of obesity has not as yet been fully studied. Other endocrine glands, such as the gonads, the adrenals, etc., certainly participate in it. The adrenal cortex can be cited as an example of similar, but even more complex, hormonal interrelations in patients with obesity.

According to the data of Kazakhov[5] with obese patients, a decrease in the formation and excretion of urinary 17-ketosteroids and a tendency toward increase in total corticosteroids and glucocorticoids are observed. Thus, even more complex disturbances of the hormonal relations are demonstrated here, according to the type of glandular dysfunction.

TABLE I

Changes in the Functional Activity of the Insular Apparatus and Thyroid Gland

Changes in functional activity	% of demonstrated deviations from normal of usual clinico-biochemical tests	% of demonstrated deviations from the normal of special tests	Demonstrated pathologic disturbances
Increased activity of beta cells in the pancreas	Increase or decrease of the blood-sugar level in 20% of the cases	Hyperinsular type of reaction of the sugar curves in 60% of all cases	Prediabetes in 8% of the cases
Decrease of functional activity of thyroid gland	Reduction of basal metabolism in 41% of the cases	Evidences of I^{131} after 24 hrs reduced in 85% of the cases	Clinically demonstrated hypothyreosis in less than 10% of the cases

Tissue Metabolic Disturbances

Finally, the local tissue factor plays an important role. We certainly cannot support the mechanistic theory of Bauer (cited by Leites[6]) on isolated "lipophilia" of the tissues of patients with obesity. However, the factors in metabolic disturbances in the fatty tissue proper are interconnected with the disturbances of the nervous and endocrine system and are capable of acquiring an important pathogenetic role in the development of obesity. In studying the permeability of capillaries according to Landis, Levitskii[7] demonstrated that the interrelations between tissue and blood metabolic processes in obesity patients are very complex. He likewise demonstrated the presence of increased permeability of the capillaries by sodium chloride, water, and, to a lesser extent, serum proteins, sugar, and cholesterol.

It was established long ago that fat tissue is not inert and possesses rather considerable metabolic activity.[8] Nonetheless, a more detailed biochemical characterization of these processes has only recently become possible. In the fatty tissue itself a number of changes actively occur—the hydrogenation and dehydrogenation of fatty acids and the conversion of glucose into glycogen and fat. It has been demonstrated experimentally that in obesity a number of these processes are clearly altered. For example, the formation of fat from carbohydrates is increased, and the enzymatic breakdown of carbohydrates is blocked. There is a further tendency to explain a number of disturbances in corpulent patients by the presence of peculiarities of local tissue metabolism. For instance, in the deposition of fat and glycogen, insufficient sugar is utilized by the tissues. This leads to hyperglycemia, but, because of the interoceptive signaling, responsive alterations of the neuroendocrine system take place: the excitability of the alimentary nerve center increases, the production and flow of insulin into the blood become greater, and so forth.

The neural-endocrine-metabolic disturbances observed to some degree in all cases of obesity exclude the possibility of purely exogenic forms of obesity. The "gluttony" and "indolence" of corpulent patients are endogenically stimulated, but the biochemical shifts in these patients are still not always discerned, because of our imperfect knowledge.

CLINICAL COURSE

In obesity a change occurs in the life activity which is due to the influence of the neural-endocrine-metabolic disturbances; the course of the primary life processes—circulation, respiration, and digestion—is altered. As mentioned, these changes are connected on the one hand with changes in the processes of central regulation, and on the other with secondary anatomic and functional modifications of tissues and organs. For example, the character of the atherosclerotic disturbances in obesity is linked with the fact that they arise and progress on a background of already pronounced dystrophic disturbances. The reactions to this superimposition proceed at a considerably slower rate. Hence, advanced coronary atherosclerosis produces phenomena of functional insufficiency, attacks of angina pectoris, etc., at a relatively later time. The somewhat benign course of atherosclerosis in obesity and the relative ease and speed of improvement in the condition of these patients dictate the need of unremitting, energetic treatment in the earlier stages of adi-

posis. A number of electrocardiograms have shown clearly pronounced coronary insufficiency that disappeared after a short period (1–2 months) of diet therapy. The same response has occurred in cardiopulmonary insufficiency and in disturbance of the peripheral circulation.

The digestive organs are also affected by obesity. Here are often found rather persistent changes in gastric secretion and motility. Hyperacidity and often hypersecretion are characteristic; they proceed, however, with few signs or symptoms. Gastritis and ulcers are rare. The pancreatic enzymes in obese patients are subject to qualitative shifts, and as the observations of Dzhelieva[3] have attested, changes occur in the quantitative ratios of the basic enzymes amylase, lipase, and trypsin.

In contrast to gastric secretion, which in obesity tends to increase, both gastric and, especially, intestinal motility decreases. Colonopathy is a quite frequent complication and, in considerable measure, develops in proportion to the degree of obesity. Hypokinesia and dyskinesia of the gallbladder and bile ducts are common. Angiocholecystitis frequently develops, proceeding slowly with few symptoms (in up to 30 per cent of all obese women patients).

Hormonal Treatment

The adrenocorticotropic hormone (ACTH) has been used in our clinic for treatment of certain complications in obesity patients. We have been convinced of the good effect of this hormonal preparation in a number of patients, not only in regard to complications (principally bone and joint) but also in regard to general muscle tonus.

Kazakhov[5] gives a basis for thinking that the organism of the obese patient reacts in a unique way at introduction of ACTH. After average therapeutic doses we have not observed any increase in weight, as is noted in subjects with normal metabolism, and only a certain reduction in rates of weight loss in our patients. Apparently the latter was connected with the retention of water by the tissues, since later an increase of diuresis and a faster rate of further weight loss occurred. We noted especially effective action of ACTH in women in the climacteric or preclimacteric period.

Hormonal therapy, entirely a prospect of the future, has not yet developed a preparation for practical use. The fat hormone, adiposin, obtained in 1955 by Leites,[9] still has not gone beyond the experimental laboratory.

Nutritional Measures

At the level of our present knowledge, nutritional therapy is the principal method of treatment in all cases of obesity. On the basis of earlier observations and of our own recent works, the temporary reduction in caloric intake to the level of the patient's basic metabolism, and sometimes even lower, still remains the rule. This decrease, in the main, should result from sharp reduction of carbohydrates and, to a lesser degree, of fats. The amount of proteins should remain at the level of the physiologic norm. To facilitate carrying out this diet, feeding should be fractional (five to six times a day). On the basis of much clinical experimentation, the diet[10] worked out in the Clinic has been fully approved. The composition of the diet is cited in Table II.

This diet provides for the gradual reduction in caloric value of the therapeutic feeding (for diets No. 1 and No. 2 and their variants). The amount of table salt is also reduced, and extracts that boost appetite are banned.

Construction of such a diet facilitates normalization of the overactive insular apparatus, lowers the excitability of the alimentary center, and heightens the specific dynamic action of the food. However, even this diet is effective for only a comparatively short period of time. For further weight reduction it is necessary to use the impact effect of unilateral zigzag diets or slimming diets. Unilateral diets, comprising mainly one of the basic foods (proteins, fats, carbohydrates), lead to a quicker reorganization of the metabolism and act favorably on the central nervous system, the cardiovascular system, and the liver.

As a result of the course of treatment carried out, the patients lost, depending on the degree of obesity, 6–29 kg in weight, i.e. from 10 to 15 per cent of their weight. [In this course of weight reduction, the slimming foods used

TABLE II

Diets for Obesity (Chemical Composition and Caloric Value) and Their Variants[a]

	Proteins (%)	Fats (%)	Carbohydrates (%)	Caloric value variants A	B	C
Diet No. 1 (test)				2000	2400	2700
Caloric value	18	28	54			
Diet No. 2 (slimming)				1250	1500	1660
Caloric value	28	44	28			

[a] Part of table has been omitted.

were: meat, pot cheese, sour cream, other milk products, and apple. Over a two-month period, weight reduction was achieved by starting the patient on "one-food slimming days"—only meat for the first ten days, only pot cheese for the next seven days, then either meat, curdled milk, or apple for one day each—then giving two of these foods per day thereafter. For the course of treatment the average weight loss of the men was approximately 14 kg, that of the women approximately 10 kg. In obesity, considerable weight losses not only are harmless, but lead to considerable functional improvement of the nervous system, the cardiovascular apparatus, the gastrointestinal tract, and other systems and organs.

Types of Diets

Of the various diets used recently for treatment of obesity, that of Pennington[6] may be mentioned. This asymmetrical diet with drastic restriction (almost complete exclusion) of carbohydrates is a far departure from the physiologic norms of nutrition, and tolerance of it by patients for more or less prolonged periods is poor. Hence, it may be regarded as only for exceptional cases or short periods of treatment.

The impact effect of weight reduction in obesity can be attained in three ways: (1) by slimming days, which are extensively used in the first variant of our diet, (2) by contrast periods in dietetic management (this method is used for some food allowances in foreign countries and is being studied in a new diet variant at our clinic), or (3) by fasting diets or a course of therapeutic fasting. We are testing its use in our clinic.

We shall not dwell in detail on slimming days, since they have been discussed repeatedly and are extensively put into practice. For slimming purposes we used mainly the so-called protein days (pot cheese, meat), more rarely carbohydrate (apples and vegetables), and very rarely fat (sour cream, cream). The number of slimming days in the course of therapy occupied only about one-third of the whole period of the patient's stay in the hospital.

The use of frequent slimming days against a background of dieting, although it led to good therapeutic results, was not always tolerated equally well by the patients. Our diet, moreover, underwent special processing to eliminate purines, a matter that did not contribute to improving its savory properties. Because of this, prolonged use of such a diet ran into difficulties now and then. A follow-up of long-term results revealed that only 35 to 40 per cent of our patients were able to maintain this diet for a prolonged period. This was especially difficult for the younger groups of patients. Therefore, the question was raised of creating a more easily tolerated diet without restriction of purines and, consequently, with more acceptable savory properties.

The creation of special contrast periods in dietetic manage ent permits, if not avoidance of slimming days comple ly, at least their curtailment considerably. The most distinctly expressed multiform, zigzag periods in dietetic management proposed for treatment of obesity patients is Kannengieser's French diet schedule.[11] This diet has been used with success in England. The intent of the diet is to include different "unvaried" days in the weekly menu according to the following scheme.

Monday—vegetable day. About 2 kg of different vegetables, 100 g of black bread, 5–10 ml of vegetable oil.

Tuesday—meat day. 300–400 g of meat for the day as a whole with addition of vege-

tables and fruits (broiled beef, no sauces, and no gravy).

Wednesday—egg day. 5 eggs with addition of vegetables and 50 g of black bread.

Thursday—milk day. 1500 ml of milk with addition of 150 g of black bread and 200 g of potato.

Friday—fish day. 400 g of boiled fish with vegetables, fruits, tea or coffee, 100 g of bread for the day as a whole, and vegetable salad.

Saturday—fruit day. Fruits (except nuts, bananas, and grapes), mainly apples and pears, up to 1.5 kg.

Sunday—free selection of food, but limiting fats and avoiding large portions of meat and fish.

During the 2-to-3-month course of treatment the patients lost about 15–20 kg of weight [the author does not cite total statistics]. No doubt, such a course of diet, varied for the week and unvaried for the day, is rather difficult to carry out.

Proceeding from the principle of obtaining more varied regimens, recently in the Clinic of Medical Nutrition of the Institute of Nutrition, USSR, Prostiakov set up a new modification of the diet for obesity, in which an increase is specified of protein and purine food components with ordinary culinary preparation. Thanks to this, the taste properties of the diet have been improved and the diet is made less monotonous. It has also succeeded in reducing the number of slimming days. This diet is in the stage of experimental clinical testing.

Finally, the observations made in the Clinic on the use of therapeutic fasting should be mentioned. We do not make reference to the use of fasting as a therapeutic method, since this is an antiphysiologic method and, in addition, is not always without harm to patients. However, in some cases we did proceed to include fasting days in the diet, or even short periods of fasting (up to 5 days, especially in the younger subjects).

At the suggestion of the Academy of Medical Sciences, USSR, we also made observations on the use of longer periods of therapeutic fasting. Five of the patients with obesity who had expressed a desire to subject themselves to this method of treatment went on a 15-day course of fasting. Results were calculated in weight lost by these patients and by five patients of an analogous type who were treated by our diet with slimming days. The therapy with fasting yielded no advantages in weight loss, since at their emergence from the period of fasting considerable weight increase is noted in the patients.

The dietetic method worked out in the Clinic of Medical Nutrition and stated above, in the vast majority of cases, rather effectively reduces the weight of patients and considerably improves their general state. On the basis of observations of patients hospitalized repeatedly and of those ambulatory who are patients for a much longer time, we are able to note good tolerance of even greater losses of weight (up to 40–50 kg over a $1^1/_2$-year period). In the majority of cases of obesity the prognosis for cure or considerable improvement is entirely favorable.

The chief duties of the physician during treatment of obesity are recommendations and checking of the precise weight ratios in the diet, observation of the patient's weight (daily is desirable), as well as active psychotherapy. The physician should aid the patient in his psychologic re-education, which is requisite for proper continuing therapy and maintenance of the designated feeding and living regimen. The processes of normal inhibition of the alimentary center are developed only with the active participation of patient and physician.

A system of prophylactic measures is made the basis for rational combating of obesity, as well as of many other metabolic diseases—proper assembling of food products, a normal systematic course of diet, proper exercise, hygiene suitable to the age of the patient, early clinical care of patients with obesity, and extensive culturally enlightening work. All this aids proper functioning of the organs and normal metabolism and helps prevent overeating and physical inertia.

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Folic Acid Metabolism

A Review*

A. V. TRUFANOV†

FOLIC ACID as such is rarely encountered in living cells; it exists there chiefly in the form of its derivatives. Several biologically active forms of folic acid have been found in nature. Three natural forms of folic acid are distinguished from each other by varying amounts of the glutamic acid residues contained in the molecule:

(1) The fermenting factor in *Lactobacillus casei* (pteroyltriglutamic acid) is distinguished from folic acid by two additional residues of glutamic acid joined at the gamma-position; this compound was isolated[1,2] from the fermentative yeasts and obtained synthetically.[2]

(2) Bound folic acid (pteroylheptaglutamic acid) is distinguished from folic acid by six additional residues of glutamic acid; it was isolated from yeasts.[3]

(3) The factor of *Streptococcus faecalis* (pteroic acid) is distinguished from folic acid by the absence in the molecule of residues of glutamic acid; this compound was isolated from natural sources and also obtained synthetically.[4,5]

The most prevalent natural form of folic acid is essentially different from the first three. It was first discovered in 1948[6] in natural products (liver, rice bran, and yeast extracts) in investigations of the factors of growth necessary for *Leuconostoc citrovorum* and thus called the *Leuconostoc citrovorum* factor, abbreviated to leucovorine, or folinic acid.

Folic acid, added to the nutritive medium for *Leuconostoc citrovorum* in place of leucovorine, even in large doses does not stimulate the growth of this microbe to the same degree as do small amounts of leucovorine. Further biologic and chemical studies[7,8] of the factor of *Leuconostoc citrovorum*, or leucovorine, isolated from the liver, showed that it is the formyl derivative of 5,6,7,8-tetrahydrofolic acid. This was also confirmed by the synthesis of this substance from folic acid.[9]

Synthetic leucovorine proved to be identical with the natural factor of *Leuconostoc citrovorum*.[10] Study of the structure[10–12] of leucovorine showed that the formyl group was joined to the atom of nitrogen in position 5 of the pteridine part of the molecule. The structural

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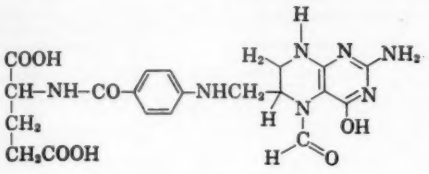
* Original title: Physiological Effect of Folic Acid and Its Metabolism in the Animal Organism in Various Diets (Fiziologicheskoe deistvie folievoi kisloty i ee obmen v zhivotnom organizme v zavisimosti ot sostava diety—obzor literatury).

† Moscow, USSR.

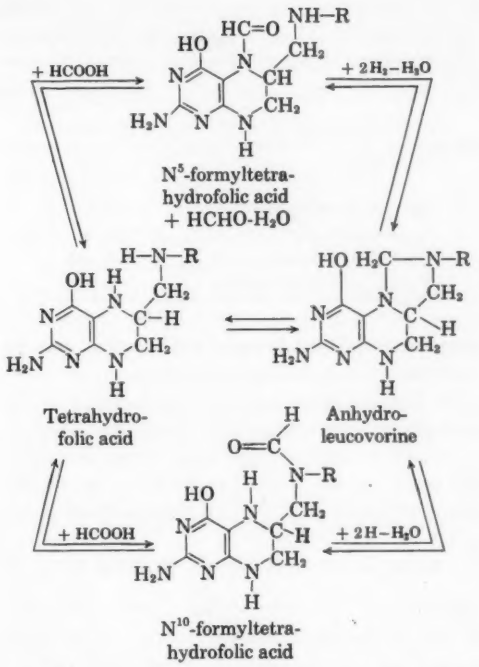
formula of leucovorine is shown below.



In an acid medium the hydroxyl group in position 4 of the pteridine part of leucovorine takes on a ketone character and makes the formyl group in position 5 more mobile; thus in an acid medium leucovorine, splitting off its formyl group, is converted to the reduced leucoform of folic acid.[7,8] The biologic activity of the synthetic product with respect to *S. faecalis* is approximately one-fourth that of the natural product. This occurs in consequence of the formation of a new asymmetric center at the carbon atom in position 6 upon reduction, as the result of which there is formed a mixture of the two stereoisomers, of which only one is active.[13a] Processing with acid and subsequent oxidation of the ring removes this new asymmetric center and thus elevates the activity with respect to *S. faecalis* to the level of activity of folic acid.

From autolysates of horse liver, isolation was achieved of N^{10}-formyltetrahydrofolic acid (N^{10}-HCO-FAH_4*).[13c] Extracts of pig liver, upon incubation in methanoic acid, adenosinetriphosphate, and tetrahydrofolic acid, convert the latter to N^{10}-HCO-FAH_4, which was isolated from the products of incubation.[14] Hence it is possible that there exist in nature two formyl derivatives of tetrahydrofolic acid—N^5 and N^{10}. The suggestion has been made[15–18a] that upon reduction, both leucovorine N^5-HCO-FAH_4 and N^{10}-HCO-FAH_4, are converted to compounds with the tetrahydroimidazole ring (anhydroleucovorine) according to the scheme at top right.

Anhydroleucovorine may be converted again into either the N^5- or the N^{10}-compound of formyltetrahydrofolic acid.



Folinic acid (leucovorine), just like folic acid, exists in nature in the combined, microbiologically inactive form: autolysis under anaerobic conditions liberates free leucovorine.[18b] It has been found that cells of *B. subtilis*[19] or *S. faecalis* upon incubation with folic acid[20,21] synthesize 5-formyl-5,6,7,8-tetrahydropteroyl-γ-glutamyl-γ-glutamyl-glutamic acid or the triglutamic homologue of leucovorine.

As confirmation of the conversion of bound folic acid to its formyltetrahydro- derivative, one may look at the experiments of Dietrich, Monson, and Elvehjem[22] in which pteroyldi- and pteroyltriglutamic acid were converted into the corresponding formyltetrahydro- derivatives upon incubation with chicken liver slices with insufficient folic acid, with the same ease of conversion as the free pteroylglutamic acid.

In the same way as folic acid can be freed by the action of the enzyme of chicken pancreas (at pH 7.0) or the enzyme of pig kidney (at pH 4.5) from its combined form, under the same conditions leucovorine is also liberated from its combined form.[19,23,24] Apparently the combined form of folic acid may be converted

* In the author's nomenclature tetrahydrofolic acid is abbreviated FAH_4; formyl was indicated by CHO, which has been changed in this article to HCO to conform to current practice.

TABLE I
Biologic Activity of the Natural Derivatives of Folic Acid

Compound	Requirement for semimaximal growth (μg/ml medium)			Requirement for growth of chicks	
	S. faecalis	*L. casei*	*Leuconostoc citrovorum*	(μg/100 g food)	μg per day
Folic acid	0.18	0.09	30,000	25	5
	0.25	0.055		75	
Fermentative factor	4.20	0.061	—	110	—
Bound folic acid	125.00	11.00	—	70	—
Factor of *S. faecalis*	0.045	140.00	—	—	—
Folinic acid (leucovorine)	0.37	0.17	0.15	25	5

into the combined form of leucovorine, just as free folic acid into free leucovorine.

In Table I are presented the findings of the biologic activity of all the mentioned derivatives of folic acid (on the basis of the results of the works of Broquist *et al.*,[8] Pfiffner and associates,[3] Luckey *et al.*,[25a], and Hutchings *et al.*[25b]

BIOCATALYTIC FUNCTIONS OF FOLIC ACID

The basic biocatalytic function of folic acid is the process of transformylation. The latter consists of the conversion of folic acid into 5- and 10-formyl-5,6,7,8-tetrahydropteroylglutamic acid and in transferring the formyl residue of the obtained compound to an appropriate acceptor. Thus, tetrahydropteroylglutamic acid is the coenzyme in this process, which has a similarity to the transfer of acetyl by coenzyme A in acetylation.

Conversion of Folic Acid into Coenzyme Form and Its Role in Interconversion of Glycine and Serine: We have already indicated the capacity of microorganisms to convert folic acid into its coenzymatic form (leucovorine or a generic compound thereof). This process is enzymatic and occurs both in the presence of cells and in cell-free extracts of the bacteria *S. faecalis*[20,21,26] or of *L. casei*,[27] and also in slices or homogenates of the liver of rats and chickens.[26,28,29,30] The study of this conversion with the aid of fractions of liver homogenates, freed of mitochondria and nuclei,[31] or with purified and acetonized preparation of the liver of chickens,[32,33] has shown that for the conversion the presence is required of homocysteine, serine, adenosinetriphosphate (ATP), diphosphopyridine nucleotide (DPNH) and Mg^{++}. The formation of leucovorine occurs schematically in agreement with the following reaction:

Folic acid, or FA $\xrightarrow{+\text{DPNH}+\text{ATP}}$ tetrahydrofolic acid (FAH_4)

FAH_4 + serine → glycine + anhydroleucovorine + H_2O

Homocysteine (RSH) + serine → $RSCH_2OH$ + glycine

$RSCH_2OH$ + anhydroleucovorine → methionine + leucovorine.

This conversion is greatly enhanced by reducing agents, especially ascorbic acid. The addition of homocysteine is nonspecific and it can be replaced by any other sulfhydryl-group-containing compound (cysteine, methionine, or glutathione). In the case above the serine is the source of formaldehyde. In 1951 Braunshteyn and Vilenkina[34] showed that the conversion of serine to glycine in the rat liver and the chicken liver is completely suspended in the presence of an insufficiency of folic acid. Later Vilenkina[35,36] established the specificity of serinase for L-serine and the participation of the cofactor related to the derivative of leucovorine upon catalysis with this enzyme. The formation of this cofactor is favored by anaerobic conditions.

The studies of Blakley[15–18] and Kisliuk and Sakami[37,38] showed that the derivative of folic acid also catalyzes the reverse action of the formation of serine from formaldehyde and glycine. Tetrahydrofolic acid serves as the coenzyme both in the reaction of the formation of serine and in the splitting of it to glycine. This acid is formylated more quickly in position N^{10} than in N^5, since the antagonist of folic acid, aminopterin, inhibits the interconversion of serine-glycine in the presence of N^{10}-HCO-FA or FA, and almost fails altogether to inhibit the same conversion in the

presence of N^5-HCO-FA. The great activity of N^{10}-formyltetrahydrofolic acid in comparison with the N^5-formyl derivative was shown by Lascelles and Woods[39] upon catalysis of the synthesis of serine by the cells of *S. faecalis* R. Finally, the isolation of N^{10}-formyltetrahydrofolic acid from the products of reaction of pigeon liver extract with tetrahydrofolic acid, methanoic acid, and adenosinetriphosphate (ATP)[40] showed that the reaction of enzymatic formylation of tetrahydrofolic acid proceeds according to the following scheme:

$$HCOOH + FAH_4 + ATP \rightarrow N^{10}\text{-HCO-}FAH_4 + ADP + H_3PO_4$$

N^{10}-HCO-FAH_4 may be quantitatively converted to N^5-N^{10}-imidazole derivative of tetrahydrofolic acid, but upon heating with alkali under anaerobic conditions it is converted to leucovorine (N^5-HCO-FAH_4). This shows that N^{10}-HCO-FAH_4, apparently, is the primary product of formylation.

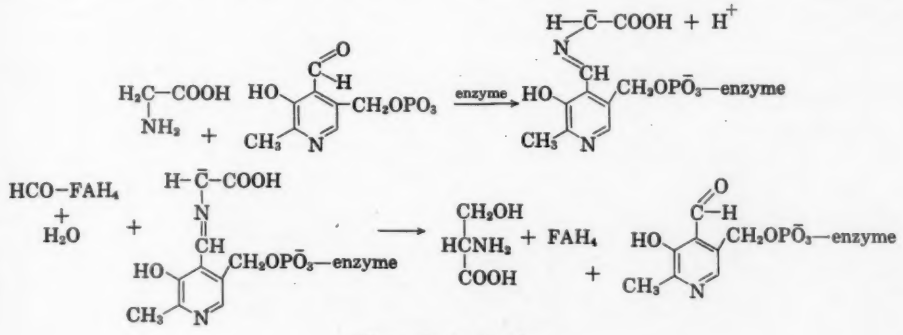
It should also be remarked that pyridoxal phosphate is a necessary cofactor in the reactions of interconversions of serine and glycine. The need for it was demonstrated[39] for the synthesis of serine from glycine by the cells of *S. faecalis* R. The absence of activating action of pyridoxal phosphate on the synthesis of serine by extracts of liver is the consequence of the presence of pyridoxal phosphate firmly bound to the apoenzyme,[15–18] which obviates the need for activating the system by the addition of pyridoxal phosphate. Extract of liver to which desoxypyridoxine phosphate is added requires pyridoxal phosphate for the synthesis of serine from glycine.[41] The role of pyridoxal phosphate in the mechanism of the biosynthesis of serine probably consists in the formation of a Schiff base with glycine, which activates the methylene carbon atom.[42,43] While in animal tissues the most active donor of formyl is formaldehyde,[15–18] in bacteria it can be replaced by methanoic acid.[20,21,39,44]

The scheme of the biosynthesis of serine is presented at the bottom of the page.

It has been established[45,46] that with folic acid insufficiency in rats there is a disruption of the biosynthesis of glycine and the conversion of it into serine. This was confirmed by the reduction of uptake of radioactivity of alanine or glucose into glycine in rats with folic deficiency;[47] in this it is accepted that the precursor of the serine is a triose.

PARTICIPATION IN THE SYNTHESIS OF PURINES AND PYRIMIDINES

In 1945, from culture of *E. coli*, isolation of an amide was achieved,[48] the further conversion of which was inhibited in the presence of sulfamide or of antagonists of folic acid. In 1947 this amide was identified as 5-amino-4-imidazole-carboxamide;[49] the authors regarded it as a precursor in the synthesis of purines. Later it turned out that in the biosynthesis of purines there is a participation not only of the free base but also of its 5-phosphoribotide.[50] Extracts of pigeon liver convert this ribotide by means of condensation with formate to inosinic acid, in which C^{14}-labeled formate is found in position 2 of the purine nucleus.[51a,b] From the inosinic acid formed by such a means, hypoxanthine can be split out. This process, as the literature referred to above has shown, is



Biosynthesis of serine

stimulated by leucovorine. From what has been said it follows that sulfonamide inhibits both the conversion of para-aminobenzoic acid into the cofactor of formylation and the process of formylation itself by *E. coli* of 5-amino-4-imidazole-carboxamide-5-phosphoribotide.[52]

The formation of 5-amino-4-imidazole-carboxamide-5-phosphoribotide itself also requires the presence of the formylation cofactor. According to current data, the mechanism of the biosynthesis of purine nucleotides begins with the interaction of ribose-phosphate with glutamine and glycine, with the formation of the aliphatic ribotide 5′-phosphoribose-N′-amide-glycine.[52] Then formylation and further conversion of this compound occur. The participation of folic acid in the formation of the formyl derivative of the given compound by extract of pigeon liver was shown by Goldthwait and associates.[53] This process proceeded only in the presence of the factor of *Leuconostoc citrovorum* or tetrahydrofolic acid. For the formation of 5′-phosphoribose-N′-amide-glycine derivatives folic acid was not required. The entire biosynthesis of inosinic acid may be expressed by the scheme at the bottom of the page.

Thus, C_2 and C_8 of inosinic acid (*IV*), marked in the scheme with an asterisk, are formed from carbon atoms of formate, which were taken into the purine nucleus under the influence of the folic acid derivative. This is proved by the constancy of the ratio of the radioactivity of C_2 to the radioactivity of C_8 in guanine-nucleic acid of rats who have received, in vivo, C^{14}-formate, both with the folic acid antagonist aminopterin and without it.[54]

PARTICIPATION IN METHYLATION

The formyl residue of formyltetrahydrofolic acid enters not only into the construction of the purine or pyrimidine skeleton; it can also be reduced to a methyl group and be transferred to an appropriate acceptor.

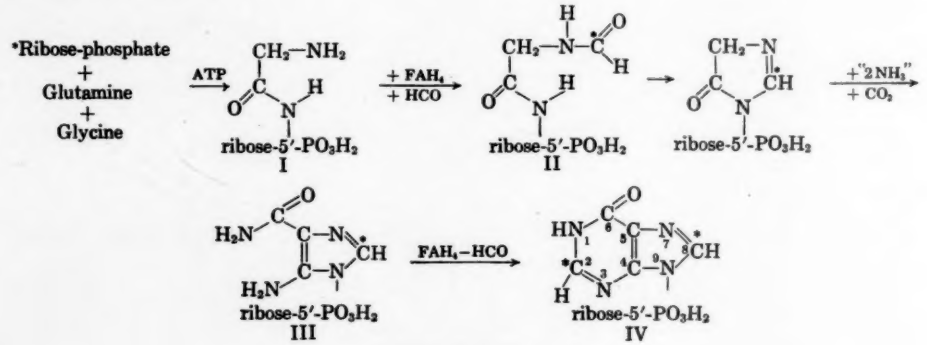
Insofar as two vitamins—folic acid and vitamin B_{12}—participate simultaneously in the formation of methyl groups, then in the absence of either of them alone in the diet of young rats, in this instance an absence of folic acid, the administration to the animals of nicotinamide causes an impoverishment in methyl groups (an exhaustion of reserves of choline and methionine in the liver), as the result of which toxicosis develops. The latter can be corrected by the administration of folic acid or choline.[55] The participation of folic acid in the formation of methyl groups also explains the diminished excretion of creatinine in the presence of a deficiency of folic acid or vitamin B_{12}. With simultaneous insufficiency of both vitamins[56] the excretion of creatinine is reduced even more sharply.

Stimulation by folic acid of the formation of methyl groups from C^{14}-formate was also shown in experiments in vitro.[57]

METABOLISM OF FOLIC ACID

The metabolism of folic acid is dependent on the administration of varying amounts of folic and ascorbic acids.

A great part of the folic acid introduced into the animal organism with the food (46 to 70 per cent) is excreted unchanged in the urine.[58] Part of it is converted in the liver into the factor



Biosynthesis of inosinic acid

TABLE II

Urinary Excretion of Folic Acid (FA) and *Leuconostoc citrovorum* Factor (CF), and Liver Content Following Subcutaneously Injected Folic Acid and Ascorbic Acid (AA)

Injected dose (mg/100 g body wt daily)	Urinary excretion (μg/100 g body wt daily)		Liver wt (g)	Content in liver		
	FA	CF		FA (μg)	CF (μg)	FA/CF ratio
—	2.7	0.025	3.3	0.55	3.3	6.0
0.05FA	17.4	0.11	3.3	0.50	3.6	7.2
0.10FA	17.7	0.10	3.5	0.40	5.8	14.5
0.25FA	53.8	0.19	3.3	1.15	6.9	6.0
1.00FA	163	0.61	3.3	1.00	8.3	8.5
5.00FA	421	2.44	3.5	2.10	9.8	4.7
20.00FA	438	3.03	2.9	8.70	8.1	0.9
0.25FA + 0.25AA	130	0.75	3.6	1.90	13.7	7.2
0.25FA + 1.00AA	223	1.27	3.6	2.31	12.3	5.3
0.25FA + 5.00AA	207	3.97	3.7	4.79	15.5	3.2
0.25FA + 25.00AA	228	3.59	3.4	6.80	10.9	1.5

of *Leuconostoc citrovorum*, and the remaining part, probably also in the liver, is subjected to enzymatic splitting and oxidation to a compound close to 6-oxymethylpteridine. The latter is confirmed by the excretion of uropterin in the urine of man.[59] With subcutaneous injections of 0.05 mg folic acid per 100 g body weight, about 30 per cent is excreted in the urine as unchanged folic acid and only 0.2 per cent as the factor of *Leuconostoc citrovorum*. Upon increasing the injected dose to 20 mg per 100 g body weight the excretion of unchanged folic acid comprises only 2 per cent, and the factor of *Leuconostoc citrovorum* 0.015 per cent, of the injected dose.[60] In contrast to that in the urine, the greater part of the folic acid accumulates in the liver in the form of the factor of *Leuconostoc citrovorum* and only 6 to 13 per cent in the form of unchanged folic acid.

Table II presents the findings on the urinary excretion of folic acid and of the factor of *Leuconostoc citrovorum* and also the liver content in young rats into which varying daily doses of folic acid and ascorbic acid had been injected subcutaneously.[60] Small doses of folic acid (0.05–0.1 mg/100 g body weight) cause only an insignificant elevation of the content of the *Leuconostoc citrovorum* factor in the liver without an increase of the amount of folic acid; larger doses of folic acid (1–20 mg/100 g body

TABLE III[a]

Influence of Composition of Diet on Content of Folic Acid (FA) and the *Leuconostoc citrovorum* (CF) Factor in the Liver

Percentage composition of diet						Weight gain of rats in 3 weeks (av. g)	Daily injection (subcutan.) of 0.25 mg FA + 5 mg AA	Weight of liver (g)	Liver content		CF/FA ratio
		Fats									
Casein	Cornstarch	Vegetable	Animal	Salt admixture	Choline				FA (μg)	CF (μg)	
18	58	10	10	4	0.01	+43	−	4.4	0.35	3.07	8.8
18	58	10	10	4	0.01	+48	+	4.6	2.43	7.70	3.2
8	68	10	10	4	0.01	+20	−	2.9	0.40	0.19	0.5
8	68	10	10	4	0.01	+23	+	3.1	2.51	1.14	0.5
8	83	5	0	4	0.01	+28	−	3.1	0.50	0.47	0.9
8	83	5	0	4	0.01	+27	+	3.4	2.45	1.41	0.6
8	68	10	10	4	0	+21	−	3.9	0.66	0.34	0.5
8	68	10	10	4	0	+20	+	3.7	2.38	1.02	0.4
0	91	5	0	4	0.01	−13	−	1.4	0.40	0.09	0.2
0	91	5	0	4	0.01	−12	+	1.4	0.63	0.24	0.4

[a] From GUGGENHEIM *et al.*[60]

TABLE IV

Symptoms of Deficiency of Vitamins of the B Group

Symptoms	Deficiency						
	Nicotinic acid		Pantothenic acid, Rats	Folic acid		Vitamin B_{12} (pernicious anemia), Man	Vitamin B_{12} and folic acid (sprue), Man
	Man	Dog		Monkey	Rat		
Leukopenia	+	+	+	++	++	+	+
Anemia	+	+	+	+	+	++	++
Bone-marrow changes	—	Megaloblastic	Hypoplastic	Megaloblastic	—	Megaloblastic	Megaloblastic
Intestinal disorders	Injured	—	Gastroenteritis	Injured	—	—	Injured
Changes of pigmentation	—	—	Abnormal	—	Abnormal	Abnormal ±	Abnormal
Disturbances of nervous system	++	++	+	+	+	+	++

+, Symptoms encountered often; ++, symptoms characteristic for deficiency of the given vitamin; ±, symptoms encountered in 50 per cent of cases.

weight) cause a more significant storage of unchanged folic acid without further elevation of the content of the factor of *Leuconostoc citrovorum*. Ascorbic acid injected with the folic acid raises the urinary excretion of both folic acid and the *Leuconostoc citrovorum* factor. Small doses of ascorbic acid raise the liver content of both factors, but with an increase in the dose of ascorbic acid the storage of folic acid is raised while the *Leuconostoc citrovorum* factor remains at the same level.

Role of Composition of Diet

Insofar as folic acid is related to protein metabolism and to the synthesis of nucleic acid, and its conversion into the cofactor of formylation (CF) is connected with an enzymatic system of protein nature, the content of protein in the diet ought to be reflected in the metabolism of folic acid. Indeed, from Table III it is evident that low-protein and protein-free diets lower the content of folic acid and especially of the citrovorum factor in the liver, and in consequence of this the ratio CF/FA falls.[60]

The data in Table III show that in protein insufficiency the ability of the liver to convert folic acid into the citrovorum factor is disrupted. Although a high content of fat in the diet and fatty liver in consequence of choline deficiency did not disturb the growth of the animal or the capacity of its liver to form the citrovorum factor, the quality of fat influenced growth in the absence of folic acid. Thus herring oil had a great influence in suppressing the growth of chicks in the presence of folic-acid deficiency in the diet, and the addition of the latter corrected this damaging action of the herring oil. Corn oil was somewhat less suppressive of growth of turkey cocks in the absence of dietary folic acid.

FOLIC-ACID DEFICIENCY

For the sake of brevity of exposition we shall not concern ourselves with the clinical manifestations of folic-acid deficiency. We shall indicate only that retardation of growth, a macrocytic anemia of the hypochromic type (in chicks), and leukopenia are the basic symptoms of folic-acid deficiency in animals. The formation of red and white blood corpuscles is connected with the synthesis of nucleic acids and depends, by the same token, on the synthesis of purine and pyrimidine bases.

As we have seen, the synthesis of purine bases and of thymine is disturbed in folic-acid deficiency; this is expressed in a reduction of the content of adenylic acid in the tissues of chicks with folic-acid deficiency.[61] In its turn, the reduction of adenylic acid content causes a reduction in the formation of coenzyme A from pantothenic acid and of cozymase from nicotinic acid. Therefore, in folic-acid deficiency in animals there may be a simultaneous appearance of the symptoms of pantothenic-

acid and nicotinic-acid deficiencies, although the diet is adequate with respect to the latter vitamins. In reality, in the tissues of rats with folic-acid deficiency caused by aminopterin it was established[62] that there was a reduced content of cozymase, which was raised by the addition of adenosinetriphosphate to the ration. On the contrary, in deficiencies of either nicotinic or pantothenic acids in rats the same symptoms were noted as in folic-acid deficiency. In Table IV the symptoms characteristic of each of these avitaminoses are compared.

It is highly probable that similar relations exist between folic-acid deficiency and deficiencies of other vitamins—riboflavin, pyridoxine, and thiamine, for the conversion of these latter into their corresponding coenzymes also depends upon the presence of the adenylic system in the tissues of animals.

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Studies on a Long-acting Vitamin B_{12} Preparation

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ABSORPTION of orally administered vitamin B_{12} is very limited and dependent upon a number of variables. For most therapeutic purposes, therefore, parenteral administration of vitamin B_{12} has proved more satisfactory.

However, the very rapid absorption and urinary excretion of vitamin B_{12} by parenteral administration[1] is considered to be a limiting factor in its therapeutic usefulness. The desirability and need for a parenteral vitamin B_{12} with delayed absorption properties has been recognized by ourselves and others.[2]

Preliminary studies toward the objective of a delayed-absorption preparation of vitamin B_{12} compared the effects of several known injectable media on absorption-excretion behavior of vitamin B_{12}. However, the degree of absorption control desired was not achieved by any of the media studied. Attention was then focused on an earlier observation that vitamin B_{12} could be complexed and insolubilized by an interaction of cyanocobalamin, zinc, and tannic acid. The repository or long-acting properties of this complex, cyanocobalamin zinc tannate‡ (Depinar§), are evaluated in the present study.

The absorption-excretion studies with this slow-absorbing vitamin B_{12} complex revealed information with possible wide implications in relation to previous concepts of vitamin B_{12} therapy.

MATERIALS

The vitamin B_{12} used in preparing the various compositions studied was crystalline cyanocobalamin, U.S.P. Comparative studies were conducted with (a) aqueous solution of vitamin B_{12}; (b) vitamin B_{12} in a concentrated (32 per cent), partially hydrolyzed gelatin vehicle; (c) vitamin B_{12} suspended in sesame oil thickened with 2 per cent aluminum monostearate; and (d) vitamin B_{12} complexed to a very insoluble form with zinc and tannic acid. The latter is referred to generically as cyanocobalamin zinc tannate, and in the text of this paper will be abbreviated as CZT. The complex was prepared in lyophilized form in multiple-dose vials, which upon reconstitution (with 5 ml sterile saline or water) provides an aqueous suspension of the insoluble complex containing the equivalent of 500 μg vitamin B_{12}, 1.2 mg zinc, and 2.6 mg tannic acid per ml. The finished suspension also contains methyl and propyl Paraben as preservatives and cysteine as antioxidant.

METHODS

Absorption-excretion studies were conducted in rats by ourselves and in humans by Best[3] and Chow.[4]

Rat Studies

Groups of eight rats (Sprague-Dawley strain) weighing 100–150 g were injected subcutaneously with 1.0 ml (500 μg vitamin B_{12}) of the appropriate preparation per rat. Pooled urine collections were made at suitable intervals for about two weeks or more. Urinalysis for vitamin B_{12} content provided an estimate of daily urinary excretion of vitamin B_{12}. We used the large (human-size) dose in rats in order to provide a more likely index as to the probable behavior of a similar dose at the human injection site. Such a large dose could

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‡ Patent pending.

§ Depinar is a registered trademark of the Armour Pharmaceutical Company, Kankakee, Illinois.

be given because of the complete lack of toxic reactions. This large dose (for rats) also provided sufficient daily urinary excretion of vitamin B_{12}, even from the CZT, to permit chemical determination of the vitamin B_{12} in urine, and thereby provided an index of the absorption-excretion rate behavior of the human-size dose. Pooled urine samples from groups of eight rats each were analyzed for vitamin B_{12} content by the method of VanMelle.[5]

Human Studies

Similar absorption-excretion studies were carried out in normal subjects by Best[3] and Chow.[4] Urine samples were analyzed for vitamin B_{12} content by microbiologic methods. Vitamin B_{12} serum level determinations were conducted by Chow[4] in which the serum samples were analyzed for vitamin B_{12} content by the microbiologic technique outlined by Gaffney *et al.*[6]

RESULTS

Several experimental lots of CZT have been studied by means of the rat excretion test, and similar experiments were performed with vitamin B_{12} in an isotonic saline solution. Table I shows a summary of the rat excretion data obtained with vitamin B_{12} in an aqueous saline solution and with three separate lots of Depinar. The data on the individual lots demonstrate good reproducibility of absorption characteristics, while the average data from the three lots provide the best estimate of the average absorption rate in rats. Analysis of pooled urine samples resulted in data which allowed only very limited statistical evaluation. Figure 1 illustrates the comparative excretion

TABLE I

Vitamin B_{12} Urinary Excretion (μg) Studies in Normal Rats Receiving Subcutaneously 500 μg Vitamin B_{12} in Saline or Cyanocobalamin Zinc Tannate (CZT)

Time after injection	Vitamin B_{12} in saline	CZT			Average ± Std. Err.
		Lot A	Lot B	Lot C	
0–6 hr	313[a]	49	52	58	53 ± 5.0
6–24 hr	23	20	18	22	20 ± 2.2
24–48 hr	5	57	21	38	39 ± 19.1
3rd day	1.3	—	—	—	—
4th day	0	44	38	47	43 ± 5.0
6th day	0	14	19	20	18 ± 3.5
8th day	0	5	9	6	7 ± 2.4
10th day	—	3	5	4	4 ± 0.8
12th day	—	1.6	4.3	1.6	2.5 ± 1.7
14th day	—	1.6	3.0	1.4	2.0 ± 1.0
20th day	—	—	1.4	—	1.4

[a] Average μg per rat; from pooled urine of 8 rats.

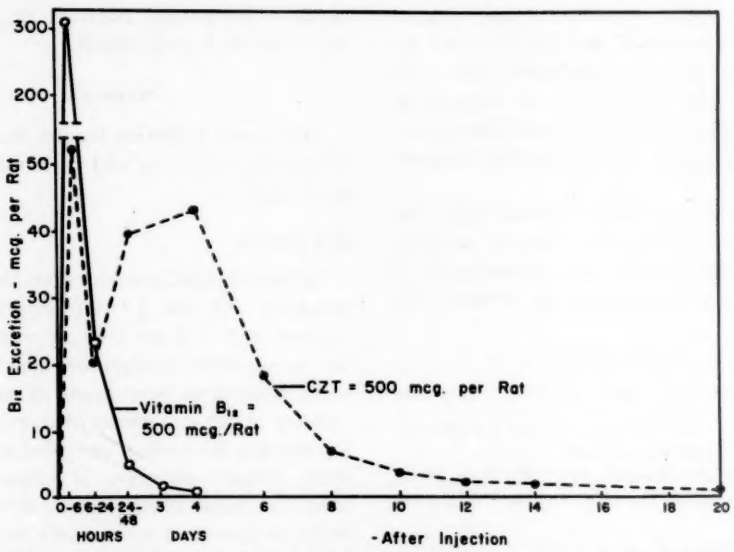

Fig. 1. Urinary B_{12} excretion after subcutaneous injection of vitamin B_{12} and CZT in rats.

TABLE II

Vitamin B_{12} Urinary Excretion Studies in Humans Receiving Intramuscularly Vitamin B_{12} (in Saline) or CZT

Hours after injection	Vit. B_{12} excreted (μg)[a] after injection			
	1000 μg vit. B_{12} in saline i.m.	500 μg vit. B_{12} in saline i.m.	CZT equiv. to 500 μg B_{12}	CZT equiv. to 250 μg B_{12}
	No. subjects			
	5	10	5	5
0–24	753 ± 43	340 ± 25	0	0
24–48	84 ± 12	0	2.4 ± 1.6	0.5 ± 0.3
48–72	1 ± 0.2	0	2.2 ± 0.6	1.5 ± 0.3
72–144	0.1 ± 0.03	0	0.7 ± 0.1	0.8 ± 0.3
144–168	0.1	0	0.2 ± 0.1	0.3 ± 0.2
Total μg excreted	838.1 ± 44	340 ± 25	5.5 ± 1.4	3.1 ± 0.5
% Excreted in urine	83.8 ± 4.4%	68 ± 5%	1.1 ± 0.3%	1.2 ± 0.2%

[a] Average ± Standard error.

rates obtained with vitamin B_{12} in saline and CZT.

Table II summarizes the urinary excretion data in humans utilizing vitamin B_{12} in saline in doses of 1000 and 500 μg, and CZT in doses equivalent to 500 and 250 μg vitamin B_{12}, respectively. The urinary excretion of the vitamin was very high after injection of the aqueous form, as contrasted with the very low excretion of the vitamin following injection of the repository form.

Figure 2 graphically illustrates the comparative urinary excretion in humans following the injection of vitamin B_{12} in aqueous saline solution, in concentrated gelatin, in sesame oil-aluminum monostearate, and in the insoluble complex CZT. The last preparation is the only one of those tested which, for practical purposes, showed almost no urinary excretion, indicating almost complete retention of the 500 μg of the vitamin by each of the human subjects. Statistical analysis of the data in Figure 2 was not attempted because of the small number of subjects involved in the tests. The results from vitamin B_{12} in saline, in sesame oil-aluminum monostearate, and in gelatin agree quite well, however, with those of Aaron *et al.*[7] Injection of vitamin B_{12} suspended in sesame

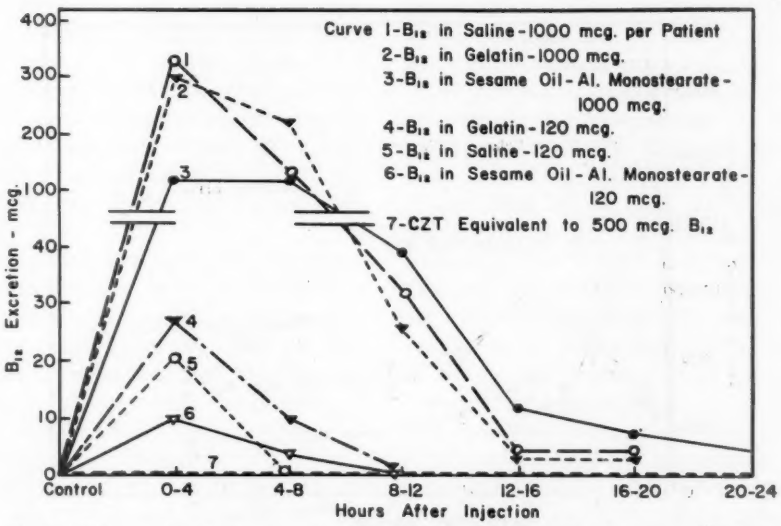

Fig. 2. Urinary vitamin B_{12} excretion after intramuscular injection in humans. Results from one or two subjects for each curve, 1–6; five subjects for curve 7.

oil-aluminum monostearate produces somewhat prolonged excretion of the vitamin, but total loss by urinary excretion is much greater than with injection of CZT. A gelatin medium apparently has very little effect on the absorption excretion behavior of vitamin B_{12}.

TABLE III

Vitamin B_{12} Serum Levels of Subjects Receiving Vitamin B_{12} or CZT by Intramuscular Injection

Days after injection	Vit. B_{12} serum levels ($\mu\mu$g/ml)[a] after injection: 1000 μg vit. B_{12} in saline i.m.	500 μg vit. B_{12} in saline i.m.	CZT equiv. to 500 μg B_{12}	CZT equiv. to 250 μg B_{12}
	No. subjects: 5	10	5	5
0	304 ± 36	340 ± 31	332 ± 61	249 ± 39
1/3	—	8026 ± 1691	—	—
1	> 9000	1728 ± 184	612 ± 138	516 ± 70
3	—	1164 ± 138	—	—
4	851 ± 67	—	868 ± 71	847 ± 106
6	—	555 ± 70	—	—
8	680 ± 78	—	1200 ± 97	1153 ± 155
9	—	446 ± 50	—	—
12	455 ± 30	—	793 ± 90	874 ± 100
16	—	—	744 ± 37	659 ± 93
21	312 ± 46	—	1060 ± 211	—
28	300 ± 37	—	692 ± 90	—

[a] Average ± Standard error.

Table III summarizes the data from vitamin B_{12} serum level studies conducted concurrently on the same subjects which provided the urinary excretion data in Table II. The temporary high serum levels obtained by vitamin B_{12} in aqueous saline were coincident with the period of high urinary excretion (see Table II). In contrast, CZT provided a marked early and sustained elevation in serum vitamin B_{12} level without producing appreciable loss by urinary excretion. The serum level of vitamin B_{12} was still significantly elevated 28 days after the 500 μg dose of CZT, while a 1000 μg dose of aqueous vitamin B_{12} resulted in the decline of the serum level to control values within about 12 days following injection. (With a 500 μg dose of aqueous vitamin B_{12}, serum levels were elevated for approximately 9 days.) The 250 μg dose of CZT provides and sustains a significantly elevated serum vitamin B_{12} level for a longer period than does the 1000 μg aqueous vitamin B_{12} dose. These comparisons are shown graphically in Figure 3.

Tissue uptake studies were conducted in rats. Radioactive vitamin B_{12} uptake was evaluated in various tissues, and the results obtained with radioactive vitamin B_{12} and radioactive CZT are shown in Figure 4.[4] Tissue uptake of radioactive vitamin B_{12} was greater from injection of CZT than from injection of an identical dose of vitamin B_{12} in saline.

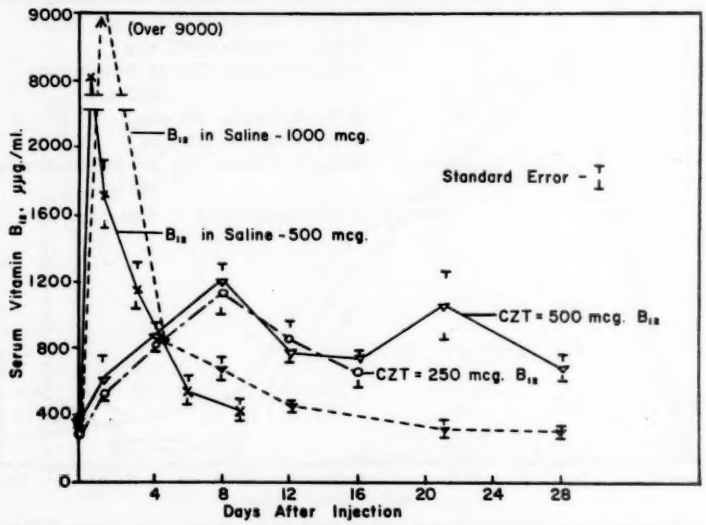

Fig. 3. Vitamin B_{12} serum levels in humans after intramuscular injection of vitamin B_{12} or CZT.

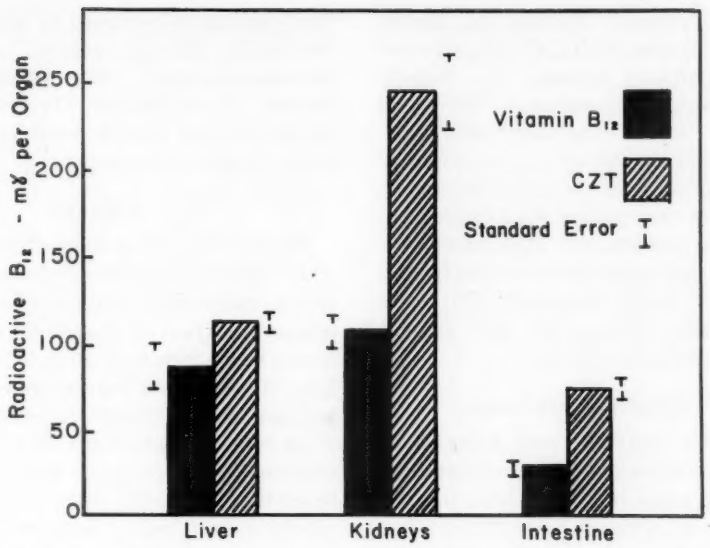

Fig. 4. Comparative tissue uptake after injection of radioactive B_{12} in saline solution and as the aqueous suspension of CZT. Normal rats sacrificed 8 days after injection of equal dosages of 0.84 μg radioactive vitamin B_{12} per rat; five rats in each group.

DISCUSSION

It has been shown that a new repository form of vitamin B_{12}, CZT, allows the administration of large doses (500 μg) of vitamin B_{12} without appreciable loss by urinary excretion. In human subjects the slowly absorbed vitamin B_{12} produces a marked elevation in the serum level of vitamin B_{12}, which is sustained for 28 days or longer following a single 500 μg injection. A certain portion of the vitamin B_{12} (about 10–15 per cent) in the CZT suspension is rapidly absorbed, as shown by the rat excretion during the first six hours after injection (see Fig. 1).

Studies designed to reflect duration of absorption of CZT suggest that serum level elevation in humans outlasts the period of absorption, which finding, in turn, suggests that the sustained serum level elevation of the vitamin is a reflection of the increased "body pool" of vitamin B_{12} accomplished by tissue uptake of nearly all of the vitamin injected.

The serum values for vitamin B_{12} are expressed in micromicrograms per milliliter, and a serum level value of 600 μμg/ml can only account for about 6 μg circulating vitamin B_{12}, as compared with about 500 μg injected. Most of the vitamin B_{12} is probably taken up by the various tissues. This view is supported by the tissue uptake studies in rats wherein the slowly absorbed CZT resulted in greater concentration of the injected vitamin B_{12} in liver, kidneys, and intestinal muscle than did equivalent doses of aqueous vitamin B_{12} (see Fig. 4).

Microbiologic assays of autopsy material by other workers[8, 9] has provided an estimate of average total vitamin B_{12} in the human body to be about 3900 μg; range 790 to 11,100 μg.

The total "body pool" of vitamin B_{12} is predominantly in the tissues, with only a minute fraction circulating in the blood stream. It is probable that the vitamin B_{12} in the tissues is largely functional rather than being present as storage of excess vitamin. It may be questioned as to whether even "average" or "normal" body pool vitamin B_{12} is necessarily optimal. Our studies show that normal subjects can retain large amounts of additional vitamin B_{12} and can even maintain serum levels several times so-called normal values without significant urinary excretion.

The capacity for additional vitamin B_{12}

retention by "normal" humans as demonstrated by our studies with CZT suggests that previous concepts of vitamin B_{12} therapy should perhaps be re-examined. It would now seem more logical that therapeutic application of vitamin B_{12} should consist of four to eight injections of CZT (500 μg vitamin B_{12} per injection) at one- to four-week intervals as convenient, to provide the opportunity for repletion of the body pool of at least 2000–4000 μg vitamin B_{12}. Such dosage of CZT could serve therapeutic, diagnostic, and insured vitamin B_{12} availability objectives.

Diagnostic and Therapeutic Applications

For diagnostic purposes, even serum level vitamin B_{12} determinations might be misleading because of the small fraction (about 0.1 per cent) of total body vitamin B_{12} in the circulating blood (about 3–4 μg vitamin B_{12} in the total blood volume on the average, against a body pool of about 4000 μg in the tissues). A slight shift in this equilibrium could theoretically cause large differences in serum level vitamin B_{12}, whether the body pool is high or low.

Due to limited absorption of vitamin B_{12} on oral administration and because of the rapid absorption and excretion of large doses of ordinary parenteral aqueous vitamin B_{12}, these modes of administration could not be expected to accomplish the above objectives for therapeutic purposes. The administration of CZT, however, appears to simulate a continuous intramuscular infusion of vitamin B_{12}, supplying the body at about the optimal rate to allow for almost total uptake by the body tissues without significant loss by urinary excretion. CZT provides long, sustained therapeutic dosage of vitamin B_{12} at the cellular level, as illustrated by the serum level and tissue uptake studies.

The above-discussed concepts of CZT therapy are especially significant as they relate to the possibility of increased beneficial effects in the fields of mental health,[10] geriatrics,[11] pregnancy,[12,13] neuropathies associated with pernicious anemia and diabetes, liver disease, alcoholism, and others. Clinical studies in these fields are planned. Initial clinical studies[14] in pernicious anemia have confirmed that vitamin B_{12} supplied in the form of CZT retains its biologic activity equivalent to vitamin B_{12} itself. Microbiologic specificity likewise is unimpaired. Preliminary studies involving use of CZT in multiple sclerosis have been reported by O'Connor *et al.*[15]

SUMMARY

Vitamin B_{12} was converted to an insoluble zinc tannate complex. Subcutaneous injection in rats caused continuous absorption and urinary excretion of vitamin B_{12} for two weeks from a single dose equivalent to 500 μg vitamin B_{12}. A similar dose injected intramuscularly in humans showed urinary excretion of less than 2 per cent of the injected dose. Serum level vitamin B_{12} was promptly elevated by several times that of control values, and these levels (above control value) were sustained for 28 days or more from the single dose.

Certain implications of these findings are discussed in relation to previous concepts of vitamin B_{12} therapy. The increased capacity of CZT injection to provide "body pool" vitamin B_{12} repletion and long-sustained elevated vitamin B_{12} serum levels makes it possible to study vitamin B_{12} therapy of a type not attainable with previous preparations of the vitamin, oral or parenteral. Clinical indications and areas for studying the therapeutic potential of CZT are cited.

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You must always be students, learning and unlearning till your life's end, and if, gentlemen, you are not prepared to follow your profession in this spirit, I implore you to leave its ranks and betake yourself of some third-class trade.—JOSEPH LISTER

Enhancement of Serum Vitamin B_{12} by D-Sorbitol

WILLIAM P. BOGER, M.D.,* DAVID S. BRASHEAR, M.D.,† AND JOHN J. GAVIN, M.S.‡

IT HAS BEEN DEMONSTRATED in animals[1] and man[2] that D-sorbitol enhances the serum concentrations that result from the oral administration of vitamin B_{12}. In a previous publication[3] it was shown that patients with subnormal serum concentrations showed prompt elevations following the ingestion of a preparation containing D-sorbitol and vitamin B_{12}. It has been postulated that D-sorbitol forms a carbohydrate complex with the cyanocobalamin, resulting in the better absorption from the gut.[1] It has also been suggested that D-sorbitol serves as a nutrient for bacteria in the gastrointestinal tract with a resultant elaboration of increased quantities of vitamin B_{12} and, consequently, a greater absorption and elevation of the serum vitamin concentrations.[4] The study here reported was undertaken to test the hypothesis that the increases of serum value might have been due to the influence of the alcohol sugar, D-sorbitol, upon the gastrointestinal flora of man.

METHODS

A group of 30 patients was selected for study, all of whom had been institutionalized for a period of at least one year and whose weight had not fluctuated by more than five pounds during this period. All the patients studied were males and varied in age from 24 to 77 years; the body weights ranged between 108 and 183 pounds. The 30 patients were divided into three groups of 10 each, and the individuals served as their own controls. The groups ran in parallel and differed in treatment only during phase C of the study. Results were determined upon the basis of differences in the average serum vitamin B_{12} concentrations observed after the daily administration of the several preparations. The medication for all three groups was personally supervised by a member of the investigational team.

The pattern of study called for four phases of observation for each patient: (A) a pretreatment control period; (B) treatment with D-sorbitol alone; (C) administration of one of three preparations; and (D) a posttreatment control period.

During phase C, group I received 1 fluid ounce (20 g) of D-sorbitol administered in divided doses at 10 A.M. and 3 P.M. each day; group II received a similar dose of D-sorbitol, combined with a solution of crystalline cyanocobalamin, so that 50 μg were administered daily; and group III received 20 g of D-sorbitol per day and 50 μg of vitamin B_{12} in the form of a prepared dosage form, Vi-Sorbin.§

Blood samples were drawn from the antecubital vein at weekly intervals from all patients in the series. Blood was allowed to clot in the refrigerator overnight; the serum was then separated, pipetted into sterile vials, and held at $-4°C$ until assayed. The *Lactobacillus leichmannii* method[5] was employed and all specimens were assayed at least twice. The specimens drawn each week were assayed as a group; then, as a check on the accuracy of method, the week-to-week results were corre-

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§ Vi-Sorbin is the trademark of Smith Kline & French Laboratories, Philadelphia, Pennsylvania, for a preparation containing crystalline vitamin B_{12} 25 μg, pyridoxine hydrochloride 6 mg, ferric pyrophosphate (soluble) 300 mg, folic acid 1.5 mg and D-sorbitol q.s., per 15 ml.

TABLE I

Plasma Concentrations ($\mu\mu$g) of Vitamin B_{12} Following Administration of Sorbitol

Patient	Wt (lb)	Age	Premedication control			$\mu\mu$g Vitamin B_{12} per ml serum							Postmedication control		
			1/30	2/6	2/13	2/20	2/27	3/6	3/13	4/3	4/10	4/17	4/24	5/1	5/15
N.C.	146	52	500	520	390	460	440	280	360	700	500	600	260	440	280
J.S.	125	68	290	260	370	180	220	160	200	300	250	200	100	220	100
C.M.	178	56	480	660	540	380	320	280	440	900	500	550	260	260	260
C.O.	169	69	120	200	200	260	160	N.S.	220	200	200	100	120	100	50
J.M.	132	73	20	160	100	120	100	124	100	100	100	120	60	60	130
E.G.	142	30	280	320	260	340	300	175	220	450	250	300	180	160	370
AVERAGE			278	353	310	290	257	204	257	442	300	328	163	207	198

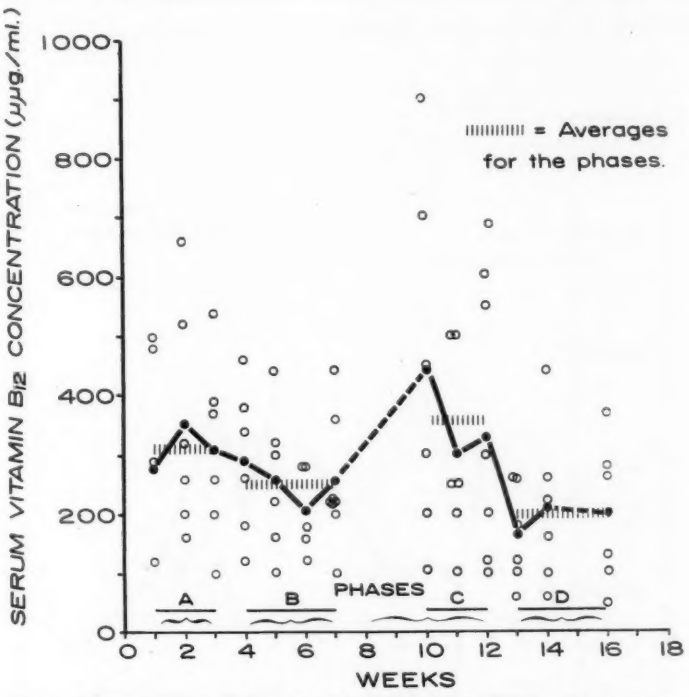

Fig. 1. Plasma concentrations ($\mu\mu$g) of vitamin B_{12} following administration of D-sorbitol alone (20 g/day).

lated by repeating a certain number of assays from the prior week. When the estimations failed to agree within plus or minus 20 per cent, the entire group of assays was repeated. Not only were weekly assays done, but upon the completion of the study all specimens from an individual patient in the series were assayed as a group on the same day. Thus every effort was made to control assay variability and to minimize its influence upon finding of difference between the treatments.

A "longitudinal" rather than a "cross-over" pattern of study was elected. This choice was dictated by previous observations that the serum vitamin B_{12} concentrations elevated by the administration of Vi-Sorbin were maintained long after discontinuance of the medication.[3] The patients in whom these observations were made had "subnormal" serum vitamin B_{12} concentrations and in this regard differed from the patients selected for the investigation reported here. Nevertheless, the

TABLE II

Plasma Concentrations ($\mu\mu$g) of Vitamin B_{12} Following Administration of Sorbitol Plus Crystalline Vitamin B_{12}

Patient	Wt (lb)	Age	Premedication control			$\mu\mu$g Vitamin B_{12} per ml serum							Postmedication control		
						Sorbitol				Sorbitol plus B_{12}					
			1/30	2/6	2/13	2/20	2/27	3/6	3/13	4/3	4/10	4/17	4/24	5/1	5/15
W.L.	183	43	300	420	520	310	280	200	460	700	450	750	450	280	N.S.
J.W.	118	59	460	200	200	100	180	100	220	500	300	400	680	320	120
W.S.	121	81	280	120	240	80	120	70	160	200	100	250	280	190	100
B.F.	125	24	220	240	200	110	140	120	220	550	350	500	180	160	150
P.Z.	113	77	520	380	860	300	460	500	J[a]	—	—	—	—	—	—
J.M.	122	53	240	480	640	380	340	280	360	650	450	650	240	240	140
AVERAGE			337	307	443	213	253	211	284	520	330	510	366	238	127

[a] Became jaundiced and was eliminated from the study.

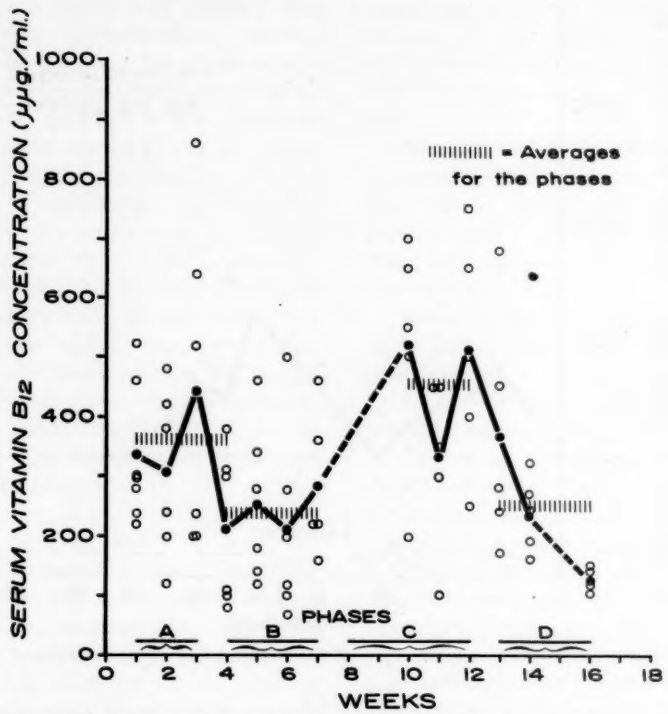

Fig. 2. Plasma concentrations of vitamin B_{12} ($\mu\mu$g) following administration of D-sorbitol (20 g/day) plus crystalline vitamin B_{12} (50 mg/day).

"longitudinal" pattern of study was selected.

RESULTS

The data are presented in Tables I, II, III, and Figures 1, 2, and 3. Of the original 30 patients selected for study only 18 could be included in the final tabulations as having fulfilled all of the criteria of full cooperation, complete blood sampling, and assay reproducibility.

DISCUSSION

In a previous study it was pointed out that for any particular individual, there appears to be a reasonably constant serum vitamin B_{12} concentration.[3,6] It has been postulated that

TABLE III

Plasma Concentrations ($\mu\mu$g) of Vitamin B_{12} Following Administration of Vi-Sorbin[a]

Patient	Wt (lb)	Age	Premedication control			$\mu\mu$g Vitamin B_{12} per ml serum							Postmedication control		
						Sorbitol				Vi-Sorbin					
			1/30	2/6	2/13	2/20	2/27	3/6	3/13	4/3	4/10	4/17	4/24	5/1	5/15
J.B.	140	48	500	300	640	180	360	180	360	750	650	700	260	320	200
T.R.	108	52	640	640	620	400	460	350	400	—	—	—	—	—	—
E.H.	142	75	300	260	320	140	200	180	220	750	300	650	240	160	110
J.M.	113	47	300	300	280	180	260	240	340	750	450	N.S.	280	280	380
R.U.	134	54	140	100	100	70	80	60	220	300	450	200	120	180	80
J.C.	155	28	440	320	320	280	200	180	240	650	250	360	240	480	200
AVERAGE			387	320	380	208	260	168	267	640	420	477	228	284	194

[a] Crystalline vitamin B_{12} 25 μg, pyridoxine hydrochloride 6 mg, ferric pyrophosphate (soluble) 300 mg, folic acid 1.5 mg, and D-sorbitol q.s., per 15 ml.

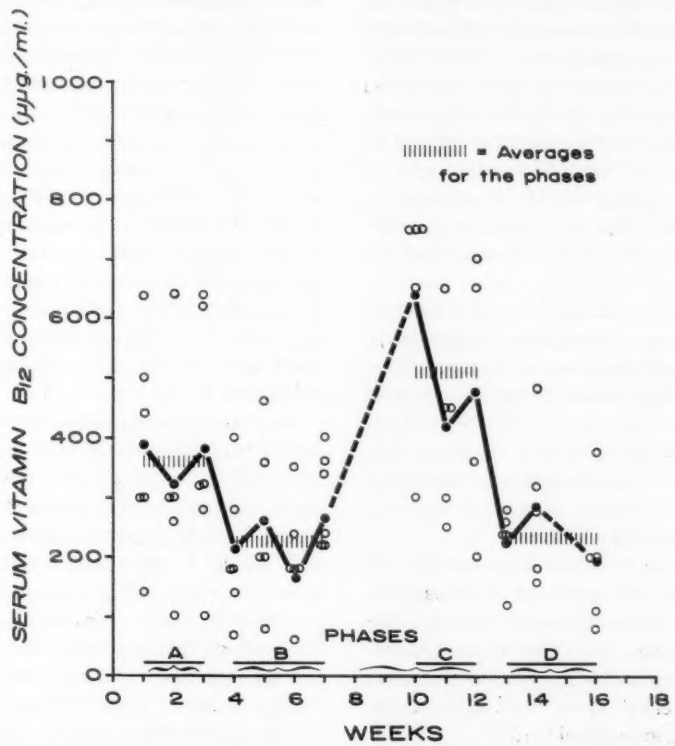

Fig. 3. Plasma concentrations ($\mu\mu$g) of vitamin B_{12} following administration of D-sorbitol (20 g/day) plus Vi-Sorbin (50 μg/day).

this relatively stable situation is a reflection of a balance between the bodily reservoirs of vitamin B_{12} and the ability of the patient to bind and transport the vitamin. In order to establish the "base-line" (phase A) against which the results of ingesting sorbitol alone or sorbitol plus vitamin B_{12} might be judged, three samples of blood were obtained from each patient and assayed for vitamin B_{12} content. In Tables I, II, and III it can be noted that a relative constancy tends to be confirmed, but there are some sharp discrepancies (J. M.,

Table I; J. B., Table II; P. Z. and J. H., Table III). Either day-to-day physiologic differences or the methodologic shortcoming inherent in a microbiologic assay can be invoked; the second alternative seems the more likely. With the exception of patients J. M. (see Table I) and R. U. (see Table III), all patients selected for this study had serum values for vitamin B_{12} that fell well within the previously defined normal range.[7] There was no explanation for the low values in these two patients. There were no evidences of hematologic, neurologic, or gastrointestinal dysfunction.

All patients in the series received sorbitol alone in the daily dose of 20 g for a period of four weeks (phase B). Powerful antibacterial substances produce alterations of gastrointestinal flora within a matter of days, but there was no anticipation that an alcohol-sugar such as D-sorbitol would produce either a prompt or profound effect. It was assumed, however, that a four-week period would be sufficient to test the hypothesis that D-sorbitol as a carbohydrate might alter the bacterial content of the gut.

Larger daily doses, based on body weight, of sorbitol have sometimes caused animals to show diarrhea and looseness of stools.[4] Similar observations have been made in man with 30 or 40 g daily doses of sorbitol. Soft stools were observed in three of our patients, but otherwise there was no indication of disturbed gastrointestinal function produced by the daily administration of sorbitol.

Tables I, II, and III show that neither the individual nor the average data of 18 patients suggest any elevation of serum vitamin B_{12} content during phase B. The serum concentrations seemed to be somewhat lower during the four-week period of sorbitol administration than in the prior control period.

During phase C, each group received a different preparation. The sorbitol group (see Table I) showed little change during an *additional* five weeks of treatment. Yet as compared with the previous four weeks on sorbitol the values tended to be higher. The group that received a supplementation of crystalline vitamin B_{12} along with sorbitol (see Table II) showed an elevation of serum vitamin B_{12} concentration above that which had been observed in the previous period on sorbitol alone (phase B) and above the original control level (phase A). The patients who received the special formulation, Vi-Sorbin, showed a greater rise of serum vitamin B_{12} concentrations (see Table III) above the control and D-sorbitol-alone periods than did either of the other two groups.

The differences between the treatments must be interpreted within the framework of the inherent error of the microbiologic assay for cyanocobalamin and the little-known factors of individual patient difference. Our assay technique has been repeatedly cross-checked with other laboratories by splitting samples and running a "blind" series of unknowns, and there is every assurance that the reliability of assay compares favorably with that reported in the literature. For this particular study, every precaution was taken to minimize assay variability as a factor in producing difference between treatments. Nevertheless, the over-all results clearly indicate that a 22 per cent variance in vitamin B_{12} assay existed. This figure exactly matches that which has been recently cited in critical reviews[9,10] as the limitation of the assay methods for cyanocobalamin.*

The assay variability as observed is regarded as unavoidable, and hence any difference between treatments must exceed this methodologic limit. Although some change in the average serum concentrations of group I (see Table I) were observed in the various phases of study, none of the changes exceeded the limits of assay variability and, accordingly, the findings of this investigation are interpreted as meaning that D-sorbitol alone produced no change in serum concentration of vitamin B_{12}.

The physiologic differences between individuals are extremely difficult to evaluate. An attempt was made in this study to select patients who had "normal" serum vitamin B_{12} values and this level was established in the pretreatment control (phase A). It can be noted that in the posttreatment control (phase

* It is worthy of emphasis that this large assay variability applies to *Euglena gracilis* as well as to *Lactobacillus leichmannii* methods.[10]

D) the values tend to be the same. In groups II and III the posttreatment levels represent a prompt decline from elevated values attained during the treatment periods with combinations of D-sorbitol and cyanocobalamin. This prompt return to pretreatment values in this study stands in contrast to the maintained elevations that were observed in our previous study of patients who had originally "subnormal" serum concentrations of vitamin B_{12}.[8]

In explanation of the difference noted between patients who had initially "normal" values and those who had "subnormal" serum vitamin B_{12} concentrations, it is suggested that reduced body reservoirs of cyanocobalamin can be replenished by the administration of a sorbitol-vitamin B_{12} combination (at least in part during a short-term study), and thereafter the serum concentrations will continue for a period of time at a more nearly normal level, even after discontinuance of medication. Such an explanation is compatible with observations that have been made of widely different rates at which serum vitamin B_{12} concentrations fall after various parenteral treatment schedules of patients with true vitamin B_{12} deficiency.

The present study, carried out in individuals who had initial serum concentrations that were declared "normal," showed that following discontinuance of the sorbitol-vitamin B_{12} preparations, the elevations of the vitamin were not maintained and the serum values returned promptly to pretreatment level. These findings parallel those made in young, healthy adults who had "normal" serum vitamin B_{12} concentrations.[8]

A low serum vitamin B_{12} concentration may reflect a modest deficit of body reservoirs which results from long-standing limited absorption of vitamin B_{12}, whether due to dietary intake of vitamin B_{12} and/or coupled with declining production of intrinsic factor of an aging gastric mucosa. In such patients, the administration of adequate parenteral vitamin B_{12} or the long-term administration of large amounts of oral vitamin B_{12} either alone or in combination with intrinsic factor or sorbitol might result in improvement of the body reservoirs and a maintenance of serum vitamin B_{12} concentrations for long periods after discontinuance of vitamin B_{12} supplementation. If one were to fully restore body depots to "normal" by any treatment, it would be anticipated that 3 to 5 years would be required for vitamin B_{12} levels to again decline to "subnormal" or "deficient" concentrations.

SUMMARY AND CONCLUSIONS

This study, undertaken to test the hypothesis that D-sorbitol might, by itself, exert a favoring effect upon serum vitamin B_{12} concentrations by an influence upon the flora of the gastrointestinal tract, has not shown such an effect. A group of 18 patients, serving as their own controls, were given 20 g of sorbitol per day for a period of four weeks; there was no observable influence upon the serum vitamin B_{12} concentration. Six patients received 20 g of sorbitol per day for an additional five weeks (total of nine weeks); no effect on vitamin B_{12} concentration was noted.

Five patients who were given daily 20 g doses of sorbitol plus 50 μg of crystalline vitamin B_{12} for a period of five weeks immediately following a four-week period during which sorbitol alone was administered showed a modest elevation of serum vitamin B_{12} concentrations.

Six patients who received treatment with Vi-Sorbin for five weeks showed even greater elevation of serum vitamin B_{12} concentrations. All 18 patients showed a prompt return to pretreatment levels of serum vitamin B_{12} concentrations when sorbitol vitamin B_{12} preparations were discontinued. This prompt return to pretreatment levels strengthens the interpretation that the changes observed during phase C of the study were due to treatment difference. It is emphasized that the microbiologic assay for vitamin B_{12}, in the best laboratories, has a variability of approximately 20 per cent.

One of the important features of the present study was the demonstration of the real difficulty of showing differences between treatments when serum vitamin B_{12} is used as a criterion. However, the findings of this study suggest that (a) sorbitol alone, in a daily dose

of 20 g, does not influence serum vitamin B_{12} concentrations; (b) D-sorbitol does appear to enhance the absorption of administered vitamin B_{12}; and (c) Vi-Sorbin seemed to elevate serum vitamin B_{12} concentrations to a slightly greater degree than did D-sorbitol supplemented with crystalline cyanocobalamin. The reason for and significance of this are not clear.

ACKNOWLEDGMENTS

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Effect of D-Sorbitol on Absorption of Vitamin B_{12} by Human Subjects Able To Produce Intrinsic Factor

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IT HAS BEEN REPORTED that D-sorbitol will enhance the absorption of vitamin B_{12} by healthy young and old subjects when the quantity of vitamin B_{12} administered is *supraphysiologic*.[1-3] The present report provides some slight support for the prior findings, but indicates that D-sorbitol does *not* regularly markedly enhance absorption of *physiologic* amounts of vitamin B_{12}. It has already been demonstrated that in pernicious-anemia patients D-sorbitol does not enhance absorption of either physiologic[1,4] or supraphysiologic[4] amounts of vitamin B_{12}.

By "physiologic amounts," we mean amounts of vitamin B_{12}, such as are found in the usual well-balanced diet, the absorption of which is mediated by intrinsic factor. By "supraphysiologic amounts" we mean quantities of vitamin B_{12} much greater than found in the ordinary diet. An aliquot of such large doses is absorbed even in the absence of intrinsic factor, probably by direct diffusion.[8]

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METHOD

The procedure, as in a prior study,[4] consisted of oral administration to the fasting subject of either 2 or 30 μg of vitamin B_{12}-Co^{58}, with or without 15 ml of a 70 per cent w/w solution of D-sorbitol in water, # concurrent administration of 1 mg of unlabeled vitamin B_{12} intramuscularly, collection of all urine for 24 hours, a second 1 mg intramuscular vitamin B_{12} injection, and a second 24-hour urine collection. The entire procedure was then repeated, deleting D-sorbitol if it had been used in the first test period or adding it if it had not been used in the first test period. Each oral dose was made up to 100 ml volume prior to administration. The amount of vitamin B_{12} excreted in the urine was determined as previously reported.[4]

The validity of repeated Schilling-type tests without a "rest period" between tests has been demonstrated,[5] and the validity of Schilling-type tests with supraphysiologic doses of vitamin B_{12} (despite the low percentage of urinary radioactivity) has been suggested.[1]

RESULTS AND DISCUSSION

Table I demonstrates that D-sorbitol may enhance the absorption of supraphysiologic (30 μg) oral doses of vitamin B_{12}, as previously reported (using 50 μg doses).[1,2] In view of the wide possible variability in sequential Schilling-type tests with supraphysiologic doses, however, four cases provide only suggestive and not

Kindly provided by E. B. Clay, Smith Kline & French Laboratories, Philadelphia, Pennsylvania.

TABLE I

Effect of D-Sorbitol on the Absorption of 30 μg of Vitamin B_{12}-Co^{58} by Healthy Young Adult Males

μg Vitamin B_{12}-Co^{58} excreted in urine

Subject	Vitamin B_{12} alone			Vitamin B_{12} + D-sorbitol		
	Day 1	Day 2	Total	Day 1	Day 2	Total
1	0.38	0.28	0.66	1.00	0.41	1.41
2	0.56	0.44	1.00	1.11	0.51	1.62
3	0.24	0.15	0.39	0.57	0.20	0.77
4[a]	0.38	0.07	0.45	0.27	0.25	0.52
[a]Average	0.39	0.24	0.63	0.74	0.34	1.08

[a] Excretion with added D-sorbitol measured prior to excretion without added D-sorbitol.

definitive evidence for such enhancement as a generally occurring phenomenon.

Table II records the effect of D-sorbitol on the absorption of physiologic (2 μg) oral doses of vitamin B_{12} by randomly selected hospitalized adults with normal baseline ability to absorb vitamin B_{12}. In the 12 subjects studied, D-sorbitol was associated with enhanced absorption in 8, no effect in 1, and decreased absorption in 3. While some enhancement by D-sorbitol is suggested in the majority of the subjects, statistical evaluation of the results does not indicate a definite general enhancing effect of D-sorbitol on absorption of physiologic doses of vitamin B_{12}.

The mechanism of action of D-sorbitol with relation to vitamin B_{12} absorption has not yet been elucidated. The available facts suggest that its action in enhancing vitamin B_{12} absorption (when it does so) is by stimulation of the gastric secretion of intrinsic factor,[6] as with carbamylcholine.[7] Just as carbamylcholine injection has raised the vitamin B_{12} absorption of "low absorbers" to normal,[7] so, in one case studied by our group, oral administration of D-sorbitol raised a low (5.8 per cent radioactive vitamin B_{12} in the urine in 48 hours) absorber of vitamin B_{12} to normal (13 per cent in the urine in 48 hours). Study of other "low absorbers," using D-sorbitol to "enhance gastric secretion of intrinsic factor," is necessary before any conclusions may be drawn, however.

It is possible that D-sorbitol may prove to be a useful agent therapeutically in the limited number of individuals whose baseline secretion of intrinsic factor is inadequate but whose gastric mucosa can be stimulated to produce normal amounts of this substance. Whether

TABLE II

Effect of D-Sorbitol on the Absorption of 2 μg of Vitamin B_{12}-Co^{58} by Adults with Various Illnesses but with Normal Baseline Vitamin B_{12} Absorption

% of Oral dose excreted in urine

Age	Sex	Diagnosis	Vitamin B_{12} alone			Vitamin B_{12} + D-sorbitol			D-sorbitol effect
			Day 1	Day 2	Total	Day 1	Day 2	Total	
63	F	Treated iron deficiency	8.4	3.6	12.0	16.4	7.5	23.9	+
34	F	Syphilitic aortitis	13.7	3.8	17.5	18.8	6.4	25.2	+
51	M	Myocardial infarction	7.5	2.8	10.3	11.1	5.7	16.8	+
58	M	Polycythemia rubra vera	7.3	3.7	11.0[a]	12.4	3.9	16.3[a]	+
34	F	Boeck's sarcoid	9.6	3.3	12.9[a]	13.4	4.0	17.4[a]	+
47	F	Subendocardial infarct	14.6	5.4	20.0	13.8	8.2	22.0	+
49	F	Diabetes mellitus	14.7	8.5	23.2	16.8	8.4	25.2	+
28	F	Cholecystitis	12.6	5.2	17.8	11.0[b]	8.0	19.0[b]	+
38	F	Lupus erythematosus	6.5	4.7	11.2	6.6	4.6	11.2	0
72	M	Arteriosclerotic heart dis.	7.9	4.1	12.0[a]	7.9	2.3	10.2[a]	−
65	F	Pleural effusion	11.4	3.7	15.1	9.1	3.7	12.8	−
35	M	Aspiration lung abscess	10.4	7.2	17.6	8.6	5.0	13.6	−
AVERAGE URINARY EXCRETION			10.4	4.7	15.1	12.2	5.6	17.8	—

[a] Excretion without added D-sorbitol measured prior to excretion with added D-sorbitol.

[b] Part of this 24-hour urine collection lost; hence enhancement by D-sorbitol actually greater than amount recorded.

it serves any useful purpose in terms of vitamin B_{12} absorption in individuals whose baseline intrinsic factor secretion is either zero or normal is questionable.

SUMMARY

D-sorbitol may enhance the absorption of supraphysiologic (30 μg) and in some cases physiologic (2 μg) oral doses of vitamin B_{12} in individuals whose ability to secrete intrinsic factor is normal. Any therapeutic utility of this agent in terms of enhancing vitamin B_{12} absorption remains questionable.

ADDENDUM

Since submission of this paper, Chalmers and Shinton (*Nature, London* 183: 118, 1959) found that D-sorbitol, in individual doses smaller than we used, had no enhancing effect on the absorption of supraphysiologic doses of vitamin B_{12} by normal subjects, as measured by serum vitamin B_{12} levels. Additionally, Heinrich, Skibbe, and Staak (*Zstchr. f. Naturforsch.* 14b: 42, 1959) reported that D-sorbitol had a measurable but therapeutically insignificant enhancing effect on vitamin B_{12} absorption by two patients with pernicious anemia, and no effect on vitamin B_{12} absorption by two normal subjects.

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Influence of D-Sorbitol on Absorption of Vitamin B_{12} by Patients with Pernicious Anemia and Achlorhydria

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RECENTLY, Chow *et al.*[1] reported on an elixir containing vitamin B_{12} that produced serum vitamin B_{12} levels in healthy young and aged people that were significantly higher than could be obtained with larger oral doses of vitamin B_{12} alone. In the same paper they reported that the elixir did not seem to be effective in treating patients for pernicious anemia.

Later studies by Chow and others[2,3] established that the absorption-enhancing factor in the elixir was D-sorbitol, a substance which is not derived from intrinsic factor. The studies also indicated that when enough D-sorbitol is administered with vitamin B_{12} there is a statistically significant increase in absorption of the vitamin by pregnant women and old people.[4] Other investigators demonstrated this unusual property of D-sorbitol in normal subjects[5] and in laboratory animals.[6–9]

Although D-sorbitol did not improve absorption of vitamin B_{12} by patients with pernicious anemia, its established ability to improve absorption in other types of patients led us to test it once again in patients with pernicious anemia on the chance that our original finding might be in error. The effect of sorbitol on the absorption of vitamin B_{12} by subjects with achlorhydria was also studied.

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MATERIALS AND METHODS

Patients with Pernicious Anemia

Twelve patients with pernicious anemia in remission participated in the study. The diagnoses of pernicious anemia were made by bone-marrow tests and by determining the amount of vitamin B_{12} excreted in the urine.

In the urinary excretion test, 2 μg of radioactive vitamin B_{12} labeled with Co^{60} (specific activity, 180 μc/mg) was administered to the patient in 30 ml of water with which the container was rinsed. Two hours later, the patient was given an intramuscular injection of 1000 μg of unlabeled vitamin B_{12}. Urine was then collected from the patient for 24 hours. After measuring the volume of urine, one half was evaporated on a steam bath until less than 50 ml remained. The amount of radioactivity in this residue was measured by a scintillation counter. Three or more months later, the test was repeated, using 10 ml of a 60 per cent aqueous solution of D-sorbitol in place of 10 ml of water.

Subjects with Achlorhydria

A total of 19 subjects with achlorhydria which was diagnosed by gastric juice analysis and/or by Diagnex¶ feeding were randomly divided into two groups. Group A (10 patients) received 50 μg of radioactive vitamin B_{12} alone, and Group B (9 patients) received the

¶ Kindly supplied to us by E. R. Squibb & Sons, Inc.; equal to quinine resin.

same amount of vitamin B_{12} together with 10 ml of a 60 per cent aqueous solution of D-sorbitol. These studies were conducted on four separate occasions (identified as studies 1–4), with the number of subjects in each group shown in Table II. Two hours later all subjects were injected with 1000 μg of unlabeled vitamin B_{12} and their urine samples were collected for 24 hours for radioactivity measurement.

RESULTS

Patients with Pernicious Anemia

Our studies with the urinary excretion test in more than 100 healthy subjects show that the average normal excretion is 11.0 per cent of the test dose of vitamin B_{12}. As shown in Table I, in the first test all patients excreted less than 1.5 per cent of the dose of vitamin B_{12}, thus confirming the diagnoses of pernicious anemia. The test with D-sorbitol demonstrated that a 60 per cent aqueous solution of D-sorbitol had no effect on the absorption of orally administered vitamin B_{12} by patients with pernicious anemia; D-sorbitol increased absorption in only 1 of the 12 patients tested (patient 5 in Table I).

Subjects with Achlorhydria

The data on the urinary excretion of subjects in Groups A and B are presented in Table II. They demonstrate that a 60 per cent aqueous solution of sorbitol enhances the absorption of orally administered vitamin B_{12} by subjects with achlorhydria. The same effect was observed in four separate studies, and the difference in the urinary excretion of radioactivity is statistically significant.

TABLE I

Effect of D-Sorbitol on the Urinary Excretion of Orally Fed Radioactive Vitamin B_{12} by Patients with Pernicious Anemia[a]

Patient	Vitamin B_{12} + water	Vitamin B_{12} + sorbitol
1	0.1	0.7
2	0.5[b]	0.5
3	0.5[b]	0.5
4	0.1	0.1
5	1.5	5.0[c]
6	0.1	0.1
7	0.5	1.0
8	0.6	1.5
9	—	1.2
10	—	1.4
11	—	0.5
12	—	1.4

[a] All results are expressed as per cent of the 2 μg of radiovitamin B_{12} given orally.
[b] Approximate.
[c] Only significant increase (low normal range).

TABLE II

Effect of D-Sorbitol on the Urinary Excretion of Orally Fed Radioactive Vitamin B_{12} by Subjects with Achlorhydria[a]

Study	Subject No.	Group A (vitamin B_{12} + water)	Group B (vitamin B_{12} + sorbitol)
1	1	1.61	2.38
	2	1.22	3.83
	3	2.14	3.17
2	4	0.51	1.91
	5	0.81	1.06
	6	1.66	2.34
3	7	1.73	1.35
	8	1.22	2.21
	9	0.56	[b]
4	10	0.65	1.83
MEAN[c]		1.21 ± 0.178	2.23 ± 0.284

[a] All results are expressed as per cent of the 50 μg of radiovitamin B_{12} given orally.
[b] Only a small portion of the 24-hour urine specimen was collected and was, therefore, discarded.
[c] Mean and standard error. The difference in the means of both groups is statistically significant ($p < 0.01$) calculated according to the Students' t test.

DISCUSSION

The finding that D-sorbitol does not increase absorption of orally administered vitamin B_{12} by patients with pernicious anemia agrees with the findings of Ellenbogen and his associates[10] and confirms our original observation.

The lack of efficacy clearly differentiates D-sorbitol from intrinsic factor, which by definition must increase absorption of vitamin B_{12} in patients with pernicious anemia. Since D-sorbitol can be effective in increasing absorption of vitamin B_{12} in patients where there is no demonstrable lack of intrinsic factor, or even in subjects with achlorhydria, it appears that there are a number of different mechanisms by which vitamin B_{12} is absorbed from the gastrointestinal tract.

SUMMARY AND CONCLUSIONS

D-sorbitol, a substance which is not derived from intrinsic factor, has been found to increase the absorption of orally administered vitamin B_{12} by certain patients who presumably possess intrinsic factor. As seen in this study, however, D-sorbitol did not increase the absorption of vitamin B_{12} by patients with pernicious anemia, but it did enhance the absorption in subjects with achlorhydria. Thus, these findings together with others[2,3] demonstrate that D-sorbitol can aid to some extent the absorption of vitamin B_{12} by all types of subjects studied except those with pernicious anemia.

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Endemic Goiter and Nutrition

I. A Study of Some Aspects of Their Relationship in a Brazilian Amazon Community

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BEFORE 1956 there was no recorded evidence of the existence of endemic goiter in the Brazilian Amazon area. During a nutritional survey in the cities of Santarém and Obidos in the lower Amazon area at the end of 1954 the author examined a number of people who presented typical diffuse enlargement of the thyroid gland suggestive of endemic goiter. In 1955 the Ministry of Health organized a nationwide goiter survey of school children in Brazil, the results of which have been published in 1956.[1] On the map accompanying this report appeared three regions in the lower Amazon with a prevalence of goiter in more than 15 per cent of males and more than 25 per cent of females. These findings are based only on rapid inspection by a physician and thus do not include smaller goiters the finding of which require palpation of the neck (grade 1 of Kimball[2] classification). One of the three areas on this map is precisely the same region of Santarém visited by the author in 1954.

Belterra, the locality of the present study, lies south and slightly west of Santarém on a plateau overlooking the Tapajoz, one of the largest southern tributaries of the Amazon River. It is a young community, only about 25 years old, and was established by Henry Ford as his second rubber plantation on the Tapajoz in 1934. In September, 1955, the author visited Belterra for the first time and made a preliminary, rapid clinical survey of 101 school children and 13 families. The children (aged 6–18) presented an extremely high dental-caries rate (100 per cent in the boys, 98 per cent in the girls) and a high percentage of diffuse goiter (62 per cent among the boys and 58 per cent in the girls). The prevalence of various other signs of possible nutritional deficiencies was much lower (thickening of conjunctiva in 23 per cent of the boys only, follicular conjunctivitis in 18 per cent of the boys and 4 per cent of the girls, follicular hyperkeratosis in 13 per cent of the boys and 22 per cent of the girls, and gingivitis in 15 per cent of the boys and 7 per cent of the girls). Among the 13 families—representing 80 persons—similar conditions were encountered: 8 families had between one and six cases of goiter per family, the great majority in the children.

After this preliminary scouting trip, which resulted in the above-presented findings, the author returned to Belterra in July, 1956, in order to do a goiter and nutritional survey among families of a random sample of the population. For this study the help of one nutritionist (SAPS†), one auxiliary dietitian (SESP‡), and one auxiliary nurse (local hospital) was obtained.

POPULATION SAMPLE AND METHODS

In selecting the sample, the administrative division of Belterra into four main divisions (zones) was maintained. A map with all the homes was obtained and 10 per cent of all homes were selected on a random basis. In case of absence or refusal (this occurred only

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two times) the home of the nearest neighbor was substituted. The final sample contained 84 families representing 426 persons (total population in 1956 was 4234)—76 bachelors who live in separate quarters were not included in the sample. The age and sex distribution of this sample was similar to the distribution of the general population (Table I).

TABLE I
Age and Sex Distribution

Age group	Male (%)		Female (%)	
	Sample	Population	Sample	Population
0–5	27.7	24.3	25.1	24.5
6–10	17.3	15.5	15.6	17.2
11–20	16.8	20.2	20.8	18.9
21+	38.1	39.5	38.3	38.8

Information Obtained

Four main categories of information have been obtained during this survey:

Socioeconomic Conditions: General information on the socioeconomic conditions of each family, including such items as income, expenses, home, and gardens. This information was obtained during the first interview by the nutritionist or auxiliary dietitian from the housewife or the chief of the family; they were recorded on the first page of the family record.

Nutrition: Specific information on the foods used by the family, the frequency of their use, and the approximate quantities used during one week. These data were recorded by the nutritionist or the auxiliary dietitian on the second page of the family record during the interview. Spot checks were made during home visits by actual weighing and measuring of amounts of foods used during one day in about 10 per cent of the families.

Physical Status: Clinical examinations were made of 413 of a total of 426 persons by the author at the local hospital, where weights and heights were taken also by the auxiliary nurse. Findings of these examinations were recorded on special forms devised by the author giving also the identifying data on each individual as well as information on his place of birth and length of residence in Belterra.

Water Analysis: Samples of water from the source of supply (a spring) and the distribution system were taken and analyzed for iodine and fluorine at the Laboratory of Industrial Hygiene in Niterói, State of Rio de Janeiro; no other laboratory work was done during this survey because of lack of help and facilities.

RESULTS

Socioeconomic Conditions

As already mentioned, the sample was selected on the basis of the administrative division of the community into four main divisions. For practical purposes, divisions III and IV have been combined, and thus the results will be presented for three separate divisions: 42 of the families came from division I (50 per cent), 14 from division II (16.7 per cent), and 28 from division III and IV (33.3 per cent). This difference corresponds to the difference in population size of the divisions. Division I represents the administrative and commercial center of town, and division II is about two miles and divisions III and IV four to eight miles from

TABLE IIA
Distribution of 413 Persons by Sex and Age Group

Age (yr)	Div. I				Div. II				Div. III and IV			
	Male		Female		Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0– 5	28	28	29	25.6	2	6.1	8	21.1	26	37.1	17	26.9
6–10	13	13	18	15.9	9	27.3	7	18.4	13	18.6	8	12.7
11–20	21	21	23	20.3	7	21.2	11	28.9	7	10.0	10	15.9
21+	38	38	43	38.1	15	45.5	12	31.6	24	34.3	28	44.4
TOTAL	100		113		33		38		70		63	

TABLE IIB
Distribution of 413 Persons by Sex and Color

	Male		Female	
	No.	%	No.	%
White	70	34.8	80	37.9
Mestizo[a]	125	61.8	119	56.4
Negro	7	3.4	12	5.7
TOTAL	202		211	

[a] Mestizos represent a mixture of either white with Negro or white with Indian, rarely of Negro with Indian blood.

the center. The mean number of persons per family in each division was five. Tables II A and II B show the age, sex, and color distribution in the divisions. Of 71 adult men (heads of families) who gave information, 23 (32.4 per cent) could neither read nor write, while 48 (67.6 per cent) had elementary schooling (three to four years).

The mean income for 82 families (for two this information was not obtained) was $1085.43 cruzeiros (about $14.00) per month, the median Cr. $810.00 ($11.50) at the free market exchange rate at that time. The range went from Cr. $750.00 to 2870.00; there were, however, only 21 families earning more than Cr. $1000 a month with a proportional distribution in each division.

The cash income was very low in 1956, but one has to take into account that all the workers' families lived in a rent-free home, were getting free medical and dental care and free drugs as needed, and were able to buy their main food items, such as meat, manioc meal, rice, and beans at the company store at reduced prices, frequently at 50 per cent of the regular market price. Even at that, almost all their cash income was spent on food, and it was not uncommon that many families, particularly the larger ones, went into debt toward the end of the month because they had exhausted their cash and had to buy on credit at the private stores where prices were much higher, as the company stores would sell only for cash.

These families tried to supplement their meager food supply by raising some animals and planting a garden. Seventy-three per cent of all the families raised a few chickens, ducks, or turkeys; some vegetables were planted by 42.9 per cent of the families in divisions II, III, and IV, but only by 16.7 per cent in division I. A greater proportion of familes (50 per cent) were planting sweet manioc, onions, rice, and leaf cabbage in division III and IV than in the other two, whereas beans were planted more in division II (25 per cent); 75.8 per cent of all families had some fruit trees, the great majority of which were banana trees, followed in frequency by orange and mango trees, except in division II where only one family had mangos. Division II was also lowest in avocado and papaya trees, while they had proportionately more guava trees. The number of families who did some hunting or fishing was negligible in all divisions.

The majority of the homes were constructed of dried palm leaf (52 per cent in division I and 85.7 per cent in division III and IV), but only 21.4 per cent were made of wood (in divisions II and IV only 10.7 per cent); 50 per cent of the homes in division II were of sheet metal (galvanized) and tile-roof construction.

Nutrition

Meat, rice, sugar, coffee, manioc meal, and beans (dried) were the main foods used almost daily by all the families in the four divisions. In regard to some of the other foods used, there were significant differences between division I on the one hand and the three divisions on the other. Bread (white wheat), oranges, lard, leaf cabbage, and canned meats and fish (sardines) were used by a significantly higher percentage of families in division I than in any of the others. Families in divisions II, III, and IV used per family more salt fish, eggs, and pork, but these differences did not reach significance. Table III is based on the results of the weekly food consumption records and shows the percentage consumption per unit of nutrition for various nutrients compared to the Recommended Daily Allowances by the Na-

TABLE III

Comparison of Percentage Daily Consumption per Nutrition Unit as Compared with N.R.C. Requirements[a] in Families of the Three Divisions in Belterra

Nutrient	Div. I	Div. II	Div. III and IV
Calories	69.0(71.4)[b]	44.0(45.5)	77.3(80.0)
Protein	85.6(108.9)	60.9(77.4)	76.4(97.3)
Calcium	16.6(19.0)	9.9(11.2)	16.8(19.1)
Iron	69.2(83.0)	56.3(66.6)	71.6(85.9)
Vitamin A	11.7(11.7)	5.3(5.3)	13.5(13.5)
Thiamine	43.2(55.5)	27.0(34.7)	46.5(59.8)
Riboflavin	36.4(70.3)	20.0(38.5)	31.3(60.0)
Niacin	52.5(67.5)	47.5(61.4)	59.0(75.9)
Ascorbic acid	154.3(231.4)	43.1(64.6)	107.3(161.0)

[a] And a revised edition for Central America.

[b] Figures in parentheses are per cent of N.R.C. requirements revised for Central America.

All calculations were based on raw food values in the SAPS tables.[5]

TABLE IV

Percentage of Persons Examined Showing Signs of Nutritional Deficiency

Sign	Division I gr. I	Division I gr. II	Division II gr. I	Division II gr. II	Division III and IV gr. I	Division III and IV gr. II
Eyes						
Blepharitis	4.2	1.0	1.4[a]	0	9.0[a]	1.5
Thickening of the conjunctiva	7.5	8.0	4.2	11.3	4.5	6.8
Spots of the conjunctiva	27.2	6.1	39.4	0	27.8	6.8
Circumcorneal congestion of the conjunctiva	39.9	2.8	40.8	1.4	38.3	2.3
Follicular conjunctivitis	5.6	0.5	4.2	0	6.8	0.8
Mouth and Tongue						
Angular stomatitis	1.4	0	1.4	0	1.5	0
Edema of the tongue	14.1	0	16.9	0	23.3	0
Fissures of tongue	4.7	0.9	2.8	1.4	3.0	0
Atrophy of filiform papillae	2.8	0	1.4	0	4.5	0
Hypertrophy of filiform papillae	38.5	2.3	36.6	0	31.6	1.5
Atrophy of fungiform papillae	6.1	0	9.9	0	9.8	0
Hypertrophy of fungiform papillae	10.3	0	9.9	0	10.5	0
Teeth and Gums						
Missing teeth	16.5	33.8	22.5	38.0	13.5	32.3
Defective teeth	33.8[a]	2.8	47.9[a]	4.2	50.4[a]	7.5
Redness of gums	16.9	0.5	14.1	1.4	28.6	0
Edema of gums	15.0	0.9	16.9	0	18.8	0
Bleeding of gums	4.2	0	2.8	0	6.0	0
Recession of gums	10.3	4.7	16.9	0	18.8	0.8
Extremities						
Curved legs	15.5	0	16.9	0	16.5	0
Increased knee jerks	0.9	0	4.2	0	1.5	0
Decreased knee jerks	4.7	0	8.5	0	19.6	0
Calf tenderness	9.4	0.5	26.8[a]	0	3.0[a]	0.8

[a] Differences between groups are statistically significant at the 5 per cent level.

tional Research Council of the U. S.[3] and a revised edition for Central America.[4] Units of nutrition* were used instead of persons because they give a more accurate picture of actual requirements according to age and sex.[6]

Physical Status

In the following will be presented the results of the clinical examination of 417 individuals for the presence of signs of possible nutritional deficiencies.

Skin: Xerosis was found in 5.4 per cent of all persons, with an equal distribution in all divisions. Follicular hyperkeratosis appeared in 8 per cent of divisions I and II and in 13.5 per cent of division III and IV.

Eyes: There was a fairly high percentage showing various eye signs, as seen in Table IV. Outside of the signs presented in Table IV there were only occasional cases with other signs, such as winged shoulderblades, enlarged liver, or curvature of the spine.

Thyroid Enlargement: There were significant differences between division I on the one hand and divisions II and III and IV on the other hand in regard to the number of persons presenting grade II enlargement of the thyroid

TABLE V

Various Degrees of Thyroid Enlargement Found

Degree of enlargement	% of Div. I	% of Div. II	% of Div. III and IV
Grade I	12.7	15.5	12.8
Grade II	14.6[a]	40.8[a]	36.1[a]
Grade III	0	0	0.8

[a] Differences between groups are statistically significant at the 5 per cent level.

* Unit of nutrition represents the amount of an essential nutrient containing the calories required by a man of 25 years of age doing moderate work in 24 hours.

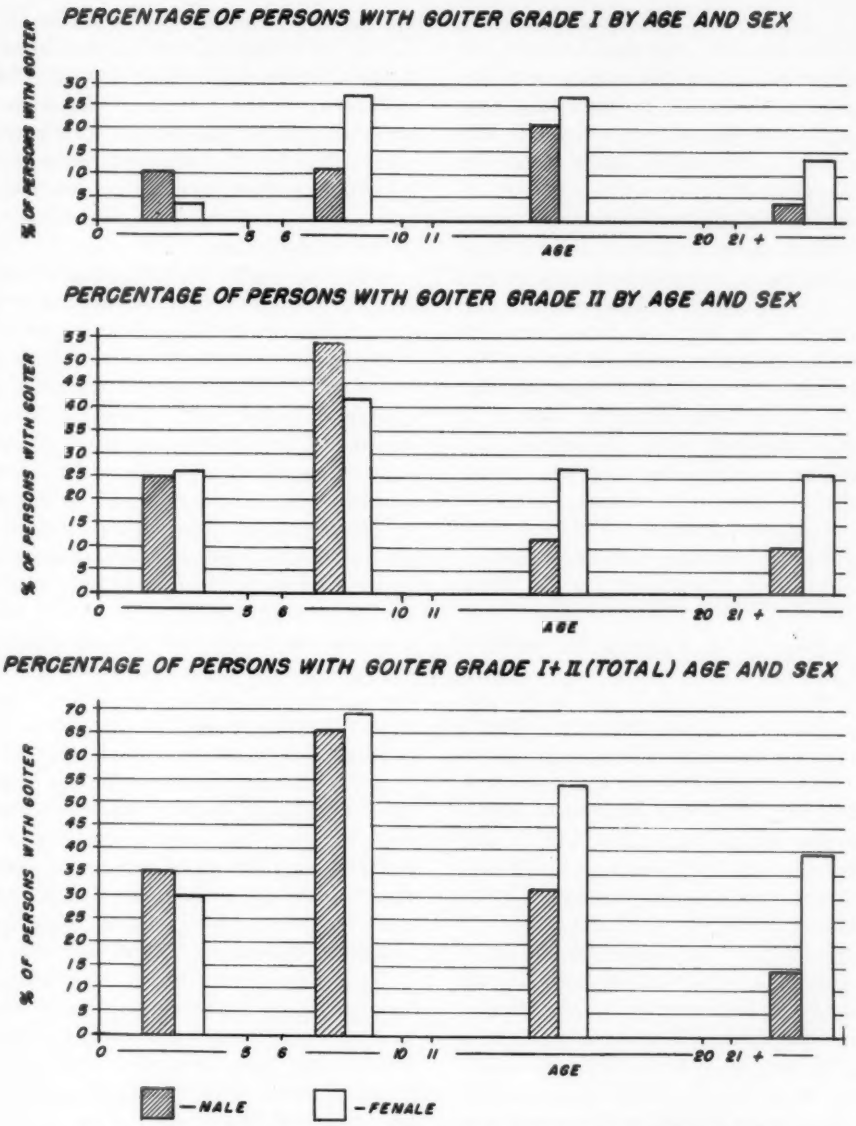

Fig. 1. Age and sex distribution of persons with goiter, Belterra, Brazil, 1956.

(following the classification by Kimball[2]), as shown in Table V.

After this significant difference in the geographical distribution of the goiter was found, the total number of cases were broken down according to age and sex (Fig. 1).

The children of both sexes between 6 and 10 years of age showed clearly the highest percentage of grade II enlargement of the thyroid; next followed the boys up to 5 years old; whereas the girls in the age group 11 to 20 had a slightly higher percentage of grade II goiter than the girls 5 years old or under. There were significant differences between adult men and women in the percentage of grade I and grade II goiters present with the latter having three to four times as many as the former.

Next, the distribution of the goiter by color

of subject was examined, and a higher percentage of grade II goiter was found among the Negro girls than among the whites, with the mestizos (pardos) second; however, the number of Negros in the sample was very small, only 19 out of 413 (4.8 per cent). There was no difference to speak of between the males of different color in regard to frequency of goiter. The birthplace of the individual did not show any relationship to the frequency of goiter; for instance, the percentage distribution of persons from the Northeast of Brazil was the same among the goiter group as among the group free of goiter. Only 14 of the 84 families were goiter-free (8 of these lived in division I); of the 70 families with goiter, 28 had one case and 42 (50 per cent) two or more cases (maximum 6).

Water Analysis showed a low pH (4.3) and complete absence of either iodine or fluorine.

INTERPRETATION AND DISCUSSION

The population of Belterra represents a fairly homogeneous economic group of rubber gatherers (seringueros) with a cash income not lower than in most parts of the interior of northern and northeastern Brazil, but with various social benefits such as free medical care, rent-free homes, and others not common to similar groups in the interior. If there was an economic factor at play in producing the picture presented, one might expect this factor to be equally strong in the four divisions.

Considering the food situation in 1956, some of the differences found between the divisions can be explained on the basis of supply. Division I was definitely at an advantage in regard to the supply of fresh beef, fish, vegetables, and fruits, because the fresh food was always brought to the administrative center first where it was sold the same day to avoid spoilage. (There was no refrigeration or even cool-room to keep perishable fresh supplies overnight.) As the supply of fresh fish, vegetables, and fruits was many times so low that it could not satisfy even the smallest demands of all families, most of it was sold in division I before it could get out to the other three divisions. That the families living in those divisions tried to help themselves to a certain extent is shown by the fact that more than twice as many families of other divisions planted some vegetables than did those of division I. They also had more room for planting, living more at the periphery where there were fewer rubber trees or none. The fact that they ate pork is explained by the fact that, because less fresh beef got out to them, they did quite a bit of butchering of home-raised pigs.

However, as Table III shows clearly, the families in division II did a rather poor job of feeding themselves; their daily intake per unit of nutrition[6] did not even reach 50 per cent of the N.R.C. requirements[3] in any nutrient except protein and iron, whereas the families in divisions I, III, and IV managed to get more calories and all other nutrients. It is true that North American standards are too high for the people of smaller than average stature living in the Brazilian tropics; but even if one uses a revision for Central America,[4] more adequate for conditions of the Brazilian North, the daily consumption of these people still remains very low for calcium, vitamin A, thiamine and riboflavin, with the families in divisions I, III, and IV doing better than those in division II.

That the nutritional situation has not changed for more than 10 years can be gauged from some unpublished data[7] of a questionnaire survey of food consumption of 150 families made in 1946. The mean caloric intake of these families per unit of nutrition per day was 2153.8 calories, which is slightly more than the calories in division I (2073 cal/day/unit).

The results of the clinical examination are puzzling, as one might expect a high percentage with various vitamin and mineral deficiencies which might have developed after such a low intake of essential nutrients over an apparently long period of time.

Signs of Deficiency

Calories: Caloric deficiency was present among many families, particularly in division II. Evidence in the form of a presentation of weight curves in relation to height and age will be presented in a later publication.

Protein: Two cases of moderately severe kwashiorkor were observed, one at the local hospital, in children between one and two years

of age. In adults and older children no evidence was found of protein deficiency.

Iron: There was no evidence of deficiency of this mineral.

Calcium and Vitamin D: If one considers the curved legs as evidence of past rickets there was some evidence in all four divisions. Clear-cut evidence of calcium deficiency was not found in spite of extremely low intakes. However, more evidence has been accumulating in recent years that suggests that our recommended requirements may be too high, because people are able to maintain metabolic equilibrium on a very low intake.[9]

Vitamin A: Except for conjunctival spots the prevalence of other classical signs of vitamin A deficiency was low in all divisions.

Thiamine: Except for a moderate amount of increased calf tenderness in division II and of diminished knee jerks in division III, the percentage of these signs in the other divisions was low.

Riboflavin: The percentage of circumcorneal congestion of the conjunctiva was equally high in all three divisions; all other signs were encountered in only very few persons.

Niacin: The signs of deficiency of this vitamin were more frequent in all divisions, with hypertrophy of the filiform papillae leading. Why the percentage of people presenting these various signs of deficiency of vitamin A and vitamins of the B-complex was not higher we are unable to explain at this time.

Ascorbic Acid: The prevalence of edema, bleeding, and recession of the gums was equally low in all three divisions despite tremendous differences in ascorbic acid intake between division II (low) and divisions I, III, and IV (very high). As most of the people presenting such gum changes were adults, a causal relationship with ascorbic acid deficiency becomes unlikely; poor oral hygiene was undoubtedly a factor in causing these changes.

Fluorine and iodine: the complete lack of both in the water supply, together with its high acidity, may be taken as an indication that the soil of this region may also be lacking in these and other minerals; this in turn may lead to a very low mineral content, particularly of iodine, in any crops raised on these soils, as has been found in other soils of endemic-goiter regions.[14] The two chief nutritional problems in Belterra, dental caries and endemic goiter, may partly be explained on this basis. Until now no analyses for iodine of such basic foods as manioc meal have been published, but they will be available soon.

Dental Caries: This was found as one of the main signs of nutritional imbalance—excess of soluble carbohydrates on the one hand; lack of calcium, fluorine, and vitamin A on the other.

Goiter: The enlargement of the thyroid found and diagnosed as simple or endemic goiter poses a very interesting question. First of all, there is the difference in geographical distribution, with a significant increase from the center (division I) toward the periphery (divisions II, III, and IV): If the nutritional picture had shown a similar distribution, i.e., if the dietary intake in divisions III and IV had been as low as in division II, this parallelism would have been more than suggestive of a causal relationship.

Age, Sex, and Color

Age: Epidemiologically speaking, the goiter in Belterra presents various features different from most studies reported in the literature. The highest percentage of total goiter was found in the 6- to 10-year-old children of both sexes, a different finding from those in Michigan[9] and São Paulo, Brazil,[10] where the highest prevalence exists during puberty. In Belterra the goiter starts already to decline during puberty.

Sex: Sex differences become marked only during puberty where goiter in boys is declining much more rapidly than in girls. This difference becomes more marked with increasing age, supporting the findings of other authors.[11–13]

Color: No great importance can be assigned to the interesting finding that the few Negro females showed a higher percentage of goiter than the white ones—because of the very small number of Negroes in the sample. No reference in the literature has been found to this respect.

SUMMARY AND CONCLUSIONS

Results of a clinical and dietary survey of 84

families representing 413 persons living in four different zones (divisions) in the Brazilian Amazon community of Belterra on the Tapajoz River have been presented.

Economically these families are a homogeneous group of rubber gatherers on a plantation established by Henry Ford in 1934 and owned and administered by the Brazilian government since 1946. They are living at a very low socioeconomic and educational level as compared to North American or West European levels, but not any lower than many of their compatriots or hundreds of millions in other undeveloped parts of the world.

Their diets, based on four or five main items such as rice, beans, manioc meal, meat or fish, and sugar (in coffee), provide a monotonous daily fare. They were found to be grossly inadequate as compared with N.R.C.-recommended daily allowances in calcium, vitamin A, thiamine, riboflavin, and niacin in all groups.

Except for such signs as spots on the conjunctiva, increased calf tenderness, circumcorneal congestion, and hypertrophy of the filiform papillae of the tongue, the prevalence of other signs of possible nutritional deficiencies was low in all groups.

Dental caries and endemic goiter present, without doubt, the main nutritional problems in Belterra, with their frequency increasing from the center toward the periphery. Outside of a suggestive correlation between the highest goiter rate and the lowest dietary intake of all essential nutrients no explanation can be given for this interesting geographical difference at this point.

Actually this study has left more questions unanswered than it was able to answer. As much further work was needed in order to find some of the answers to this puzzling goiter story of Belterra, another survey was done one year later (1957). The results of this second survey appear in Part II of this paper.[8]

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Endemic Goiter and Nutrition

II. A Follow-up Study of 75 Families in a Brazilian Amazon Community

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IN JULY, 1956, a nutrition and goiter survey of 84 families was made by the author in Belterra, a community of rubber gatherers on the lower Tapajoz river. The results of this survey formed the basis for Part I of this paper.[1] Because of the many questions left unanswered during the first survey the author went back to Belterra in July, 1957, one year after the first survey, and did a follow-up study on the same families examined in 1956 with the help of the same dietitian from SESP† and the auxiliary nurse of the local hospital as well as the laboratory technician of the hospital.

The main purpose of this follow-up survey was threefold: (1) To see whether there had been any change in the economic situation of the people after the installation of the minimum salary by the Federal Government in August, 1956, and if there was a change, how it affected the nutritional situation. (2) To observe the natural development of goiter in the same people after one year before any preventive measures (such as the introduction of iodized salt) might have been installed. (3) To investigate the relationship between goiter and dietary intake in more detail by studying individual consumption for at least one day in addition to family food intake.

POPULATION SAMPLE AND METHODS

Of the 84 families studied in 1956, nine had moved away in 1957, leaving 75, or 89.3 per cent of the original sample, to be studied anew. They represented 381 persons, 45 less than in 1956. The division of these families into three groups according to the geographical zone they lived in has not been maintained, for reasons to be explained later on.

The following data have been obtained during this second survey:

Socioeconomic Conditions: Income and prices of main food items.

Nutrition: Weekly food consumption of families during the last week of July or the first week of August, 1957. Additional observations were made by the dietitian for at least one weekday in each of 21 homes. These observations included individual food intake verified by weighing and measuring the raw foods and cooked portions.

Physical Status: Clinical examinations were repeated by the author in 347 persons examined previously in 1956. Heights and weights were rechecked by the auxiliary nurse.

Laboratory Examination of Stool: Stool samples were brought to the hospital by 229 persons and examined for the presence of parasites and eggs by the laboratory technician using the direct examination of the fresh sample.

RESULTS

Socioeconomic Conditions

For 70 families information was obtained on their monthly income. Their mean income was $2827.10 cruzeiros, the median Cr.$2300.00, or three times as much as it had been in 1956. (At the free market exchange rate at that time this corresponded to $35.00 and $30.00, respectively.) In order to see whether this sig-

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nificant increase in cash income reflected a true increase in buying power, at least as far as the main food items were concerned, the difference in cost of these items between 1957 and 1956 was determined from information obtained on how much they spent per unit weight or measure on these items in 25 families (one-third of all families studied). The results of these inquiries are presented in Table I.

TABLE I

Percentage Difference of Price Paid in 1957 as Compared to 1956

Food	%
Manioc meal	+380
Rice	+103
Beef, fresh	+300
dried	+ 25
Beans, dried	− 37
Sugar	+ 8
Coffee	+ 27

Although the prices of all foods listed were higher in 1957, with the exception of beans, the increase was not big enough (except for manioc meal and fresh beef) to absorb the increase in salary. Thus it appears safe to assume that the housewife in Belterra was able to buy more food in 1957 than she could buy in 1956.

This greater buying power in 1957 should reflect itself in the results of the weekly food consumption records which were obtained for 73 families representing 373 persons in both years (2 families did not fill in this form in 1957).

Table II shows clearly that the nutrition of these 73 families had improved considerably in 1957 as compared to 1956. With the exception of ascorbic acid (which showed a slight decrease) all nutritive values increased from 21 per cent up to 240 per cent. The increase in the mean consumption of protein, calcium, phosphorus, vitamins A and D, and the B vitamins was proportionately higher than the increase in the mean intake of calories and carbohydrates; this indicates that these people not only ate more but also had a better diet in 1957. A comparison of the daily consumption of such items as meat and fish showed that there was a highly significant increase in the amounts eaten in 1957 (Table III).

In 1956 when we compared the mean intake of 84 families divided into three groups according to their geographical location in Belterra we found that the families living in division II had the lowest intake; at the same time these families showed the highest amount of goiter. However, the families living in division III and IV, which also had a high prevalence of goiter, had a high intake of most important food items similar to the families in division I with the lowest goiter rate. After these findings we

TABLE II

Comparison of Food Consumption of Families Before and After Increase in Buying Power

Nutrient	Mean daily intake of 73 families (373 persons) 1956 Per person	1956 Per unit of nutrition[a]	1957 Per person	1957 Per unit of nutrition	% diff. between 1957 and 1956, per person data
Calories	1526	1989	1951	2552	+ 27.8
Carbohydrates (g)	291	—	353	—	+ 21.4
Fats (g)	14	—	23	—	+ 67.2
Proteins (g)	47	53	78	87	+ 64
Calcium (mg)	154	124	227	185	+ 53.9
Phosphorus (mg)	683	—	1252	—	+ 83.3
Iron (mg)	7	8	11	12	+ 47.9
Vitamin A. (I.U.)	463	564	851	1047	+ 83.7
Thiamine (μg)	450	716	967	1394	+ 93.5
Riboflavin (μg)	596	861	1412	2052	+136.9
Niacin (mg)	6	9	14	20	+115.8
Ascorbic acid (mg)	76	88	73	84	− 4.1
Vitamin D (I.U.)	4	—	14	—	+240

All calculations were based on raw food values in the SAPS tables.[2]

[a] Unit of nutrition represents a nutritive value adjusted according to age and sex of the individual.[2]

TABLE III

Daily Consumption of Meat and Fish by 73 Families in 1956 and 1957

Food	Daily consumption (g) per family					
	1956	No. using food	1957	No. using food	% increase in amount	% change in no. families using food in 1957
Fresh beef	324	68	553	69	70.6	+ 1.4
Canned meat	57	32	103	23	80.7	− 25.0
Fresh pork	66	6	200	14	203	+133.3
Salt pork	53	4	625	2	1079	− 50.0
Fresh chicken	68	2	228	18	235	+800.0
Fresh fish	214	38	362	53	32	+ 39.5
Dried pirarucú[a]	52	6	152	42	192.3	+600.0
Dried beans	210	59	352	70	67.6	+ 18.6

[a] Pirarucú = Amazon "codfish."

TABLE IV

Mean Daily Intake per Unit of Nutrition in Three Groups According to Frequency of Goiter in 1956 and 1957

Nutrient	Group I		Group II		Group III	
	1956 14 Families	1957 9 Families	1956 28 Families	1957 23 Families	1956 42 Families	1957 41 Families
Calories	2877	2915	2039	2935	1831	2357
Proteins (g)	82	106	69	106	47	79
Calcium (mg)	192	335	127	227	109	154
Iron (mg)	11	15	8	15	8	10
Vitamin A (I.U.)	662	1607	669	1007	488	973
Thiamine (μg)	928	1731	740	1498	709	1303
Riboflavin (μg)	1124	2950	1015	2005	715	1938
Niacin (mg)	13	20	10	22	9	19
Ascorbic acid (mg)	147	79	101	103	77	79

All calculations were based on raw food values in the SAPS tables.[2]

TABLE V

Comparison of Percentage Daily Consumption per Unit of Nutrition as Compared with N.R.C. Requirements[a] in the Families in Three Groups According to Goiter Incidence

Nutrients	Group I		Group II		Group III	
	1956	1957	1956	1957	1956	1957
Calories	95.9(99.2)[b]	97.1(100.5)	67.9(70.3)	97.8(101.2)	61.0(63.1)	78.6(81.3)
Protein (g)	116.5(148.3)	151 (192.2)	98.3(125.1)	151.6(192.9)	67.6(86.1)	112.9(144.5)
Calcium (mg)	24.0(27.4)	41.9(47.8)	15.9(18.1)	29.4(32.4)	13.6(15.6)	19.3(22)
Iron (mg)	95.2(114.3)	125.1(151.3)	69.9(83.9)	121.3(145.6)	62.6(75.2)	86.6(104)
Vitamin A (I.U.)	13.2	32.1	13.4	20.1	9.7	19.5
Thiamine (μg)	51.5(66.2)	96.2(123.6)	41.1(52.8)	83.2(107)	39.4(50.6)	72.4(93.1)
Riboflavin (μg)	41.6(80.3)	109.3(210.7)	37.6(72.5)	74.2(143.2)	26.5(51.0)	71.8(138.4)
Niacin (mg)	71.2(91.7)	106.5(141.5)	54.2(69.7)	123.5(158.9)	50.2(65.4)	106.5(136.9)
Ascorbic acid (mg)	196 (294)	105.7(158.6)	143.6(215.4)	136.7(205)	102.4(153.6)	105 (157)

[a] And with revised edition for Central America.

[b] Figures in parentheses are per cent of N.R.C. requirements revised for Central America.

used a different approach in our investigation of the relation between goiter and nutritional intake. We abandoned the division of families on a geographical basis and divided them, instead, into three groups according to the frequency of goiter in the families:

Group I, families without goiter.

Group II, families with one case of goiter.

Group III, families with two or more cases of goiter.

Then we compared the mean daily intake of various nutrients in these three groups (Table IV).

The differences in the consumption of all nu-

trients between group I and group III were highly significant in 1956. This picture changed in 1957, when group III improved its intake to such an extent that only calcium, vitamin A, and riboflavin showed significant differences between the two groups, whereas levels of niacin and ascorbic acid were about equal. Group II, which in 1956 stood between groups I and III in regard to its intake, came up to the level of group I in 1957 in calories, protein, and iron and even excelled group I in niacin and ascorbic acid.

In Table V the daily consumption in the three groups is being compared with the N.R.C.-recommended daily allowances[4] and also with a revised edition for Central America[5] for both years.

In 21 families (28 per cent) representing 128 individuals selected according to goiter prevalence a one-day individual diet record was kept on all persons eating in the home. The dietitian weighed the raw foods used during that day by the housewife and then weighed the cooked portions of each individual before the meal. She also noted if there were any leftovers but usually everybody ate his plate clean. Calculations of the individual consumption was done after conversion of the cooked food values back into raw values because of lack of uniformity in the preparation of certain foods (such as dried beans) and also because of lack of data on cooked foods in the Brazilian tables.[2]

The following use was made of these data: For each person above 5 years of age the daily caloric requirement was calculated by using the Mayo Foundation Food Nomogram by Boothby and Berkson which correlates surface area with basal calories; we added 50 per cent to the basal calories for all children under 12 and all adult women; for the working men and adolescents as well as pregnant and lactating women we added 70 per cent. We then compared the actual caloric intake as calculated from the one-day diet record with the requirement of each in-

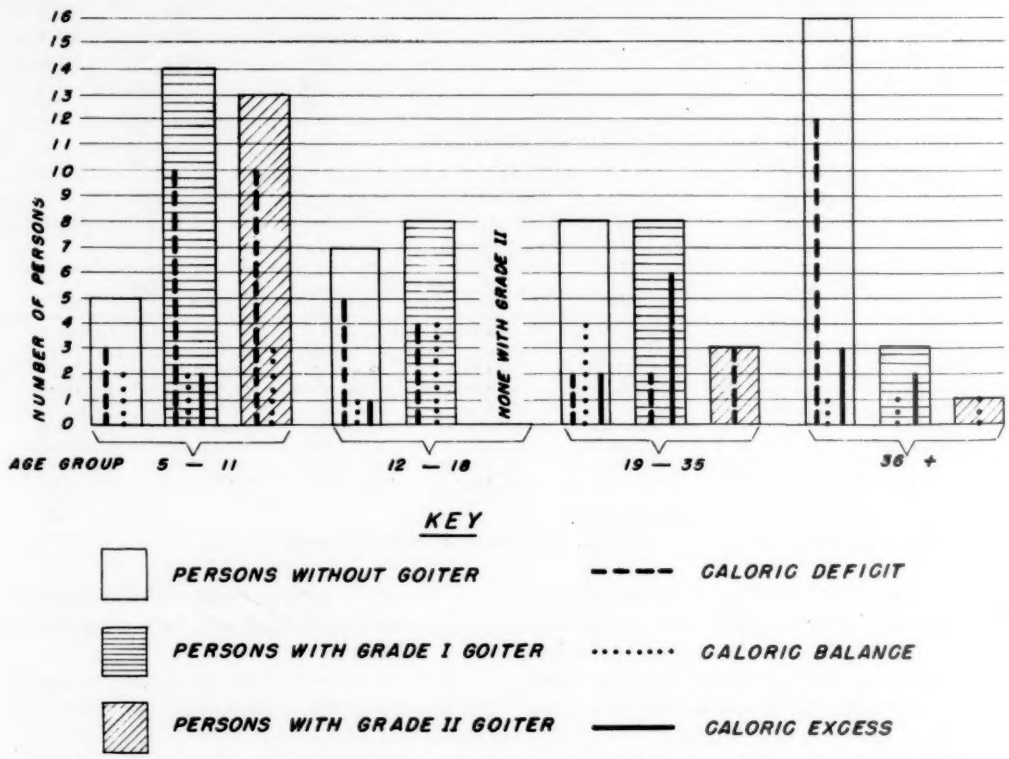

Fig. 1. Caloric intake by 86 individuals for one day in Belterra, Brazil, according to age group and goiter.

TABLE VI

Percentage of Persons Showing Changes in Some Signs of Nutritional Deficiency

Sign	1956 No.	1956 %	1957 No.	1957 %	Increase or decrease in 1957
Eyes					
Blepharitis	22	6.4	10	2.9	−
Thickening of conjunctiva	53	15.3[a]	111	32.0[a]	+
Spots of conjunctiva	124	35.8[a]	27	7.8[a]	—
Follicular conjunctivitis	21	5.1	38	11.0	+
Tongue					
Fissures	16	4.7	28	7.9	+
Hypertrophy of filiform papillae	126[a]	34.3	63[a]	18.2	−
Atrophy of fungiform papillae	26	7.5	10	2.9	−
Gums					
Redness	78	22.5	39	11.2	−
Edema	62	17.9[a]	24	6.9[a]	−

[a] Differences are significant at 5 per cent level.

dividual and thus found whether the individual ate more than, less than, or the actual requirement that day. If the actual intake exceeded the requirement by more than 10 per cent, it was considered excess calories, and if the intake was more than 10 per cent below the requirement, it was considered caloric deficit. We then divided the 86 individuals 5 years of age and older into four age groups according to goiter incidence and examined the caloric intake in relation to requirement in each group. The results are presented in Figure 1.

Among the 27 children aged 5–11 years who had grade I or grade II goiter, 74.1 per cent showed a caloric deficit; 4 of these children, in fact, had a deficit greater than 50 per cent of their requirements. In all other age groups which showed goiter the percentage of persons with a caloric deficit was much smaller, or there were not any; however, as will be noted, the total number of persons with goiter also diminished greatly with age. In the oldest group (36 years +) only 4 persons had goiter against 16 without goiter; 75 per cent of those 16 showed a caloric deficit.

TABLE VII

Incidence of Goiter in 347 Persons According to Grade and Year

Year	Grade I No.	Grade I %	Grade II No.	Grade II %	Total no. goiters Gr. I and II	% of total examined
1956	46	33.3	93	66.7	139	40.0
1957	106	65.9	55	34.1	161	46.3

Physical Status

The results of the clinical examination in the same 347 persons examined in 1956 and 1957 show some changes (Table VI). In all other signs looked for about the same percentage of people was found presenting the sign as in 1956 (see Table III in Part I of this paper).[1]

The general incidence of the endemic goiter found in 1956 showed some interesting changes (Table VII). Although there was a slight increase in the total goiter incidence of 6.3 per cent, the percentage of grade II goiters decreased more than 40 per cent in 1957, whereas the percentage of grade I goiters increased correspondingly to 56 per cent. In order to see what happened to all those persons who presented goiter at any one time in 1956 or 1957 a graph was prepared (Fig. 2). As can be seen 45.7 per cent of those individuals who showed grade I goiter in 1956 were found *without* any goiter in 1957; out of the people with grade II goiter in 1956, 38.7 per cent presented only grade I goiter and 20.5 per cent *no goiter* at all in 1957. Only 40.8 per cent of those with grade II goiter remained grade II in 1957, and of those with grade I goiter, 43.5 per cent stayed grade I, whereas 10.9 per cent became grade II in 1957. Of the individuals who in 1956 were free of goiter and developed

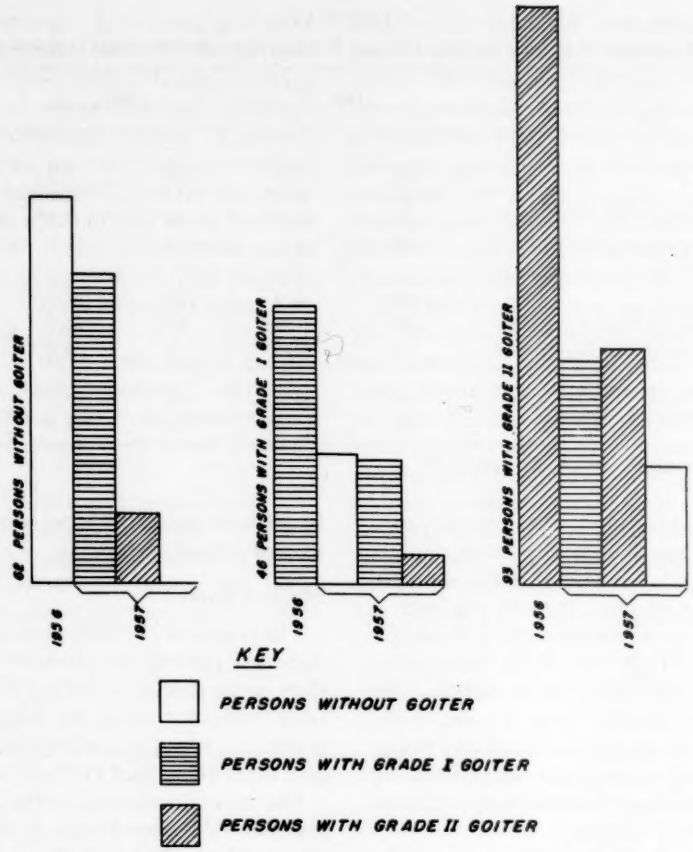

Fig. 2. Results of examinations of 201 persons in Belterra, Brazil, examined in 1956 and 1957 in regard to prevalence of goiter.

a goiter in 1957, 80 per cent developed a grade I goiter and 20 per cent a grade II goiter.

Laboratory Findings

The results of the stool examinations in 229 persons (66 per cent) showed all of them infested with eggs (83 per cent showed ascaris and trichuris eggs), some with parasites (9.6 per cent with strongyloides) and 3.1 per cent carrying cysts of either *Giardia lamblia* or *Entamoeba histolytica*.

INTERPRETATION AND DISCUSSION

There can be no doubt that the introduction of a minimum salary by law on August 1, 1956, improved the economic situation in Belterra sufficiently to give greater buying power to the families. That this increased cash income made people buy more and better food and, thus, led to a significant improvement in their diet at the time of the follow-up survey has been shown unequivocally. There is good reason to assume that this improvement is continuing as long as prices of the main foods can be kept at the 1957 level. According to recent information obtained on the spot (October, 1958), this is still true. It should be emphasized in this connection that this beneficial effect of the minimum salary observed in Belterra is peculiar to this community. It would be wrong to generalize from this unique situation.

Considering the comparison of mean daily intake in the same 73 families in 1956 and 1957 (as presented in Table II), it is obvious that in

spite of the considerable increase in almost all nutrients in 1957 the values for calcium and vitamin A still remain very low. The increase in protein and the B vitamins, however, is impressive and, as Table III demonstrates, is derived mainly from animal sources. This indicates that the improvement in the diet was going in the right direction; however, experience by many nutrition workers in various parts of the world teaches that an educational program including home gardens is necessary in order to correct the remaining deficiencies, such as of calcium and vitamin A in the case of Belterra.

Differences in mean daily consumption between family groups divided according to their geographical location in 1956 were found much more pronounced when the same families were grouped according to goiter prevalence among them. The association between higher goiter prevalence and lower intake of practically all nutrients which was very strong in 1956 was still present in 1957, even though the intake of all nutrients except ascorbic acid had increased considerably in group III—the families with the highest goiter prevalence. That the intakes of most nutrients in all three groups had become adequate or even better than adequate in 1957 can be gauged from the comparison with N.R.C.-recommended daily allowances in Table V; only calcium and vitamin A still remained very low.

That vitamin A deficiency per se may be associated with an increase in goiter, not only in endemic goiter areas, has been shown by Haubold[6] among children in Upper Bavaria and Lubeck, Germany, after the war. Clements,[7] in a study of food consumption of 112 families in a goiter area in Australia, also found the intakes of vitamin A and calcium unsatisfactory, whereas he found the values for calories, protein, iron, vitamin B_1 and ascorbic acid satisfactory according to N.R.C. requirements. However, in his group there was no relation between dietary inadequacy and the incidence of goiter among children.

Bergfeld,[8] in an endemic goiter area in Oberbaden, South Germany, found a correlation between goiter frequency and the relative proportion of certain nutrients in the diet. In his group "goitrous" families consumed more fats and proteins of animal origin than did the "non-goitrous" families, where more carbohydrates in the form of bread and pastries and vegetable fat such as margarine were used. It is however, not stated whether, even with such differences in proportions of these main nutrients, the diets of the "goitrous" and the "non-goitrous" families were adequate in regard to vitamins and minerals. It would be also essential to know the kind and quantity of vegetables these two groups consumed. The same author did some feeding experiments in rats with diets corresponding to the diets he found in the families studied. The fact that the rats on the high-protein and high-fat diet developed enlarged thyroids, which were preventable with a sufficient relative increase of the carbohydrate portion in the diet, whereas the thyroids of the rats on the high-carbohydrate diet remained normal until they received five times as much fat and meat as before, shows that a strong *imbalance* existed in the goitrogenous diets of these families.

Obviously, if the diets of the Belterra families showed any imbalances, they were in contrast to the ones demonstrated by Bergfeld; carbohydrates and proteins of vegetable origin predominated in the Belterra diets, although there was a definite improvement from 1956 to 1957. Dried beans have been found goitrogenous if given in large amounts to experimental animals;[9] people in Belterra certainly consumed a great amount of those. None of the numerous other foods,[10] principally of vegetable origin, which have been recognized as potential goitrogens, were eaten in large amounts by the people in Belterra.

In an attempt to explain the apparent association between lower food intake and goiter prevalence, one fact deserves emphasis not mentioned above: Whereas the mean number of persons per family in group I was 3.3 (3.6 in 1956) it was 3.6 (3.4 in 1956) in group II, and in group III 6.2 (6.1 in 1956). This means that there were almost twice as many mouths to feed among the families in group III than in group II or group I. The goiter prevalence in Belterra, as has been shown,[1] was highest among the young children before puberty; one might call it a "children's goiter." That an

age factor is operating in this picture is further suggested from the results of the one-day individual diet records. From Figure 1 it appears as if a caloric deficit during childhood may be strongly associated with high goiter prevalence, whereas just the opposite occurs in the older adult. Whether this can be explained on the basis of a relatively higher iodine requirement during childhood remains an open question.

It is true that one-day diet records are generally not sufficient to give a good picture of the individual's average intake because of variations in the diet from day to day within one season and between seasons. In Belterra, however (as in most of northern Brazil), the diet consists of a few items which rarely vary from day to day.[1] The seven-day family food record confirmed this supposition very well in regard to quantities as well as quality of the diet. There are, however, seasonal variations in the Amazon region; they do affect the diet particularly in relation to consumption of such fruits as oranges, mangos, avocados, guavas, and pineapples. This may become very important particularly in relation to carotene and ascorbic acid nutrition. The author recalls one instance in Itaituba on the same Tapajoz river, but further upriver, where during mango season in January, 1955, the vitamin A intake corresponded to 135 per cent of the N.R.C. requirement.[11] We are justified in assuming that a similar situation prevails in Belterra, because there are many mango trees in town. Such occurrences may explain in part why we did not encounter more severe and widespread signs of vitamin A deficiency; there may have been several seasons during the year when the carotene intake at least was high, and this might have led to enough storage of vitamin A after conversion of the carotene to carry over during seasons of low intake such as encountered by the author.

This leads us into the discussion of the results of the physical examinations in 1957 as compared to 1956. Some interesting changes had taken place within this one year of improved nutrition in the same persons. The examination of the eye showed a significant decrease in spots of the conjunctiva, with a proportional increase of conjunctival thickening. This might be interpreted as a response to a higher intake of vitamin A (though still low), leading to a reversion of the pathologic-anatomic process from its more advanced stage to a less advanced stage. The diminished amount of papillar changes of the tongue is compatible with the considerable increase of the intake of the vitamins of the B complex, particularly niacin. That there was also a decrease in gum changes may seem strange at first, because of a slight decrease in ascorbic acid intake; however, as was mentioned in the first paper,[1] factors other than nutritional may have been responsible for such changes. It should be mentioned that improved protein nutrition might also have played a role in the improved gum findings.

One should certainly not expect any dramatic changes in the physical findings within one year even with an improved dietary situation, except in the case of severe deficiency syndromes such as beriberi, pellagra, or scurvy. Changes in the milder chronic deficiencies dealt with in this group (so-called subclinical deficiencies) are much slower and less dramatic when they develop, and also when they start regressing.

The goiter picture, however, presented a more dynamic aspect from 1956 to 1957. There was in 1957 a spontaneous regression of goiters found in 1956 in 40 of the 139 cases (28.8 per cent). There were several families in which in 1956 four members had presented grade I or II goiter and in 1957 only one member had goiter. The author at first did not believe his own results and went to the homes of three families in order to confirm the results of his first examination; he was able to confirm them in every instance. Without knowing anything about the possible results of the dietary findings two families volunteered the information that their nutritional situation had improved greatly within that year. Also remarkable is the fact that 36 persons (26 per cent) showed a regression of their goiter from grade II to grade I in 1957, whereas only 17 persons (8 per cent) developed a grade II goiter in 1957. One is justified in concluding that, even though there was a slight increase in the over-all goiter incidence, the goiter had regressed either completely or

diminished in size in 1957 in 54.7 per cent of the total found with goiter in 1956.

Such findings are not completely surprising if one reads some of the conclusions reached by McCarrison and Madhave[12] after many years of painstaking observations in the field and on experimental animals in India:

> The thyroid is not an organ whose size is inalterably fixed but one that may vary from year to year, from season to season, or it may be from day to day, in accordance with the needs of the tissues for its product. There is normally a marked tendency to thyroid increase in the earlier years, the gland reaches its maximum weight relative to that of the body just before puberty, but there is no stable biometric constant of variability associated with thyroids under all conditions.

According to McCarrison[13] diet is the most important factor influencing the size of the gland, and the question of balance is highly important. Among other goitrogenic factors McCarrison names unsanitary conditions of life and iodine deficiency. That diet and unsanitary conditions (e.g., worm infestations) were at play in the Belterra goiter picture this paper has tried to show. Whether iodine deficiency was also a factor is not known at this time.

SUMMARY AND CONCLUSIONS

A follow-up survey was done in 75 families of rubber gatherers in Belterra, a rubber plantation on the Tapajoz in the Brazilian Amazon area one year after the first survey.

The economic situation in 1957 had improved with the introduction of a minimum salary in 1956, raising the extremely low mean cash income to about three times its previous level. As prices of the main foods did not increase to the same extent (except for meat and manioc meal), there was a real increase in buying power.

The nutritional picture improved correspondingly, reflecting the economic improvement. Except for vitamin A and calcium, which still remained low, the intake of the other nutrients compared favorably with N.R.C.-recommended daily allowances; even better with a revised edition for Central America. The increase in protein was largely from animal sources (meat and fish). There is valid reason to believe that this improvement is going to continue as long as prices can be kept at present levels (October, 1958).

The improved dietary intake was reflected to some extent in a significant decrease of such signs as conjunctival spots and papillar changes of the tongue, signs suggestive of deficiencies of vitamin A and niacin. However, as the incidence of most signs compatible with nutritional deficiencies was found relatively low in 1956, no great change would be expected within one year even on an improved diet.

Dental caries and endemic goiter still remain the principal problems of public-health nutrition in Belterra in 1957. The goiter picture, however, showed some interesting changes, possibly due to dietary improvements. There was a complete regression of goiter from 1956 to 1957 in 28.8 per cent and a regression of grade II goiter to grade I in an additional 26 per cent, whereas 29.8 per cent who had shown no sign of goiter in 1956 were found with goiter in 1957.

An association between high goiter incidence and low caloric intake in one group of families in 1956 was found more pronounced if the families with two or more cases of goiter were grouped together regardless of geographical location in town. In 1957 this association still existed but, due to general improvement of diet, was less pronounced. That age was a determinant in this relationship was shown from the results of the one-day individual diet records where there was a high association of goiter with caloric deficit in the age group 5–11 years, whereas this association disappeared in the older age groups. However, more work is needed with a larger population sample and diet records of more than one day (preferably one week) in order to clarify the significance of this relationship.

The results of this study might suggest that one has to be more careful in evaluating the effect of specific measures, such as iodized salt. The almost complete disappearance of goiter in the Great Lakes region in the United States over a period of 25 to 30 years has been ascribed to the use of iodized salt exclusively; however, one should certainly keep in mind the general improvement of the nutrition of the people over the same period as a possible factor in this result. The results of the study in Bel-

terra strongly suggest that a general improvement in the diet contributes to a change in the goiter picture.

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Diet Therapy

Dietary Patterns of the Puerto Rican People

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WITH THE steady increase of Puerto Rican population groups living in the continental United States, especially on the Eastern Coast, it seems quite timely that we write about our food habits in the hope that it will be of interest to physicians, nutritionists, and dietitians working with such groups, and of help in understanding the nutrition needs of their patients.

Puerto Ricans enjoy eating many foods that are used in the States as well as in France, Italy, or Spain. A good *biftec* (beefsteak) with fried potatoes, or baked ham, broiled fish, fried chicken, a piece of cake, apple pie, ice cream, and other dishes of the international cuisine are served every day in homes that can afford such delicacies, but this involves only a small proportion of Puerto Rican families.

TYPICAL DIETARY

Rice, legumes, *viandas* (starchy vegetables), milk, *bacalao* (dry salted codfish) are used by everyone in Puerto Rico. The low-income group will use large amounts of the first three—rice, beans, *viandas*—but little milk and codfish. With increase in income more milk is used and more dried codfish. Meat is liked very much, but being expensive is taken only once in a while by the low-income groups; the well-to-do, however, use large quantities of it every day for both lunch and dinner. Pork and chicken are favorite meats with all income groups.

Viandas are boiled whole or in large pieces and served hot with boiled dry codfish plus oil and vinegar. This is a one-dish meal for the poor, especially in the rural areas. We have many different *viandas* (see Table I) but the most popular ones are green bananas and green plantain. The ripe bananas eaten in the United States are used in Puerto Rico as a vegetable when green, before any sugar is formed. We think they are delicious with fish or meats in place of potatoes. The other most frequently used *viandas* are sweet potatoes (a grayish-white vegetable), ripe plantain and white *ñame* and white tanier. Bread fruit (panapén) is used quite a bit in some sections of the Island. *Yuca* (cassava) is not eaten as frequently due to fear of getting the variety which contains a poison. This is unfortunate for *yuca* is very nutritious (see Table I). When *viandas* are eaten as the only dish, the serving is a plateful. Some codfish is always added. When avocado is in season it is a fine addition, and when income permits, hard boiled eggs are also added. Sliced raw onions are frequently one of the ingredients used in this dish. It is a humble dish, but it has a romantic name, for it is called *serenata* (serenade).

Viandas are low in protein, calcium, and vitamin A with one exception, the plantain, which is fairly good in vitamin A; 100 grams will furnish 1,400 i.u. However, the *viandas* supply fair or good amounts of the B vitamins and iron when eaten in quantities. For example, when 1,000 or more calories are consumed in a day, as is not uncommon, these

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TABLE I
Nutritional Value of Viandas*
(Per 100 g of Food)

	Water %	Calories	Protein g	Fat g	Carbohydrate g	Ca mg	Fe mg	Vitamins A i.u.	Thiamine mg	Riboflavin mg	Niacin mg	Ascorbic acid mg
Apio (arracacha)	74.8	93	1.4	0.1	21.7	59	1.0	286	0.07	0.06	—	—
Batata blanca (white sweet potato)	71.0	110	0.13	0.15	26.9	18	0.9	53	0.09	0.03	0.7	28 (11)
Batata amarilla (yellow sweet potato)	68.2	122	0.51	0.28	29.4	22	0.8	200	0.10	0.04	0.8	39 (23)
Batata mameya (deep yellow sweet potato)	70.2	113	1.6	0.1	26.3	29	0.4	12000	0.09	—	0.7	17 (9)
Malanga (dasheen)	75.0	88	2.0	tr.	20.0	25	1.0	40	0.05	0.06	0.4	tr.
Piche verde (variety of green banana)	69.3	121	1.1	0.3	28.5	4	0.8	tr.	0.03	0.02	0.6	16 (4)
Ñame blanco (white yam)	69.3	116	2.9	0.2	25.7	11	1.2	5	0.05	0.03	0.4	8 (4)
Panapén (breadfruit)	67.9	122	1.6	0.4	28.0	15	0.8	50	0.10	0.07	1.0	23 (12)
Papa (potato)	77.8	83	2.0	0.1	19.1	11	0.7	20	0.11	0.04	1.2	17 (15)
Plátano maduro (ripe plantain)	67.5	125	1.0	0.1	30.1	3	0.9	1080	0.05	0.04	0.7	11 (3)
Plátano verde (green plantain)	57.5	165	1.1	0.2	39.8	3	0.5	1400	0.08	0.05	0.5	20 (7)
Yautía blanca (white tanier)	67.5	126	1.7	0.3	29.0	9	0.5	25	0.13	0.03	0.5	10 (3)
Yautía amarilla (yellow tanier)	61.4	155	2.8	1.4	32.9	13	0.7	350	0.40	0.04	0.9	18
Yuca (cassava)	57.2	165	2.0	0.1	38.9	27	0.9	tr.	0.09	0.03	0.4	29 (16)

* In the column for ascorbic acid numbers in parentheses indicate the probable value after vegetable is cooked as determined by C. F. Asenjo *et al.* The values are taken from a table prepared by the Home Economics Dept. of the University of Puerto Rico except for potato which have been taken from *Composition of Foods—Raw, Processed, Prepared*, Handbook No. 8, Bureau of Home Economics and Agriculture, Washington, D. C., 1950.

foods supply at least protective amounts of thiamine and niacin and very fair amounts of riboflavin. They even furnish enough vitamin C to prevent scurvy, as shown by the analyses made by Dr. C. Asenjo *et al.* of our School of Tropical Medicine. Sometimes the *viandas* are cooked with meat into a sort of soup called *sancocho* which is inexpensive and satisfying.

The next most popular foods are rice and beans. These foods are used extensively twice a day by most families except the very poor rural families, who have them only once. The higher income households also use them daily. The per capita consumption per day for rice is nearly seven ounces, which shows how much we depend on this cereal for our daily food; the per capita for beans is three to four ounces a day. Rice is cooked in small amounts of salted water and lard is added. It is called white rice (*arroz blanco*). Shiny, polished rice is preferred, but this has to be enriched according to the Puerto Rican law. It is eaten along with stewed legumes (*granos*), such as chick-peas, navy beans, pigeon peas, dried peas, and red kidney beans, the latter being preferred. They are boiled until tender and then cooked with *sofrito*. This is a tasty mixture of tomatoes, green pepper, onion, garlic, salt pork, lard, and cooking herbs (*recao*). Rice is prepared in many other ways, one of the most popular one being with legumes added, or with chopped vienna sausages, pork sausages, or dry codfish. This recipe calls for *achiote* (*annato*) coloring, which gives a yellowish color to the rice.

When rice is cooked with chicken it is called *arroz con pollo*. This is one of our superb dishes and is usually eaten with red stewed beans as an accompaniment. This dish is often prepared with an ample amount of water

so that its final consistency is that of a thick soup. This is called *asopao*.

Other Cereals

Wheat flour in the form of bread, noodles, and spaghetti as well as oatmeal are used extensively by all income groups. Cornmeal, made into mush with water or milk added, is very popular. When rice is not available cornmeal is used as a substitute and is then eaten along with beans or stewed with codfish. Oatmeal is used as breakfast food. It is always cooked with milk and is much thinner than the continental variety. Cream of wheat and other popular breakfast cereals in the States are used only by the higher income families.

Milk and Coffee

Practically all Puerto Ricans like milk and will use it when they can get it. Upper income groups use it liberally, but many among the low-income groups cannot afford it except in small amounts. Most of the milk, except for children, is used in coffee.

Puerto Rican coffee is very different from that used in the United States. It is made from finely ground, actually pulverized, coffee. It is of the Mocha variety, as this is the kind grown in Puerto Rico. We never use blends. Puerto Ricans consider coffee brewed in the United States to be extremely weak. In well-to-do homes a coffee concentrate *tinta* is made by percolating coffee with very little water. This is kept tightly covered in a glass bottle until used. A small amount of this *tinta* is added to a cup of hot milk to make *café con leche*. In the homes of the poor the coffee generally is made by putting the coffee powder into a cloth bag and pouring boiling water through it. It is not brewed as strong as it is in the well-to-do homes, but it is always much stronger than the coffee in the United States, or looks so because of its black color. It can be seen that one of the difficulties for a Puerto Rican living in the States is the acceptance of coffee prepared in the American way.

The largest part of our milk intake is thus in the form of *café con leche*. The milk is always boiled, so this insures a sanitary drink, and consequently there are few milk-borne diseases, particularly since refrigerators are being used more frequently, and because sanitary conditions have improved. People drink *café con leche* for breakfast, at three o'clock in the afternoon, and at other meals if they can afford it. A cup will have from two to five ounces of milk, the amount depending largely on the income.

Puerto Rican coffee, ground and roasted in Puerto Rican style, is available in the New York markets in the Spanish section of the city, but at a higher price than the American blends.

Other Beverages

Other favorite drinks are chocolate and cocoa. Both are made by boiling with milk and adding a lot of sugar, but no cream. Tea is not liked by the average Puerto Rican and is used only at social affairs by people of higher-income levels. Many "tea parties" are really coffee parties. One of the reasons tea is not enjoyed is that herb (green leaves) teas are used as remedies for colds or other medical purposes.

As a rule, no wine or alcoholic drinks are used at meals, but malt beer has a reputation for being very nutritious, and many ignorant mothers give it to their children, especially if they are considered to be underweight. For lactating women it is also used very generally because of the current belief that it produces milk.

Typical Day's Menu

A typical day's menu would start with *café con leche* with or without bread. This is breakfast for a high percentage of our population. Butter and an egg may be added when income permits. Oatmeal is very popular. Fruits are included at this meal only by the more educated group. In the country where bread is not available daily the inhabitants do without or will eat a piece of white sweet potato cooked in ashes. For lunch a big meal of *viandas* with codfish and oil is a very typical dish for the rural families. In the city it would be rice and stewed beans. For dinner both in the urban and the rural communities rice and beans are eaten. *Viandas* instead of bread may be an

accompaniment at this time or, when income permits, both are served.

Thus far we have been talking about the very, very poor. More prosperous families may eat stewed meat or beefsteak and add smaller servings of the *viandas*. Boiled green bananas or green plantain are used in preference to potato. Ripe plantain is quite popular as well as egg plant, and squash prepared as fritters.

Dessert is not a necessary part of a meal. Families in the urban areas may have fruit cooked in syrup or served fresh. The rural, and, as a whole, all the poor families do not have desserts. Housewives with higher incomes will serve guava paste (*pasta de guayaba*) which is made of guava pulp with a lot of sugar, or other fruit *pastas* such as *naranja* (bitter orange), *batata* (white sweet potato), *piña* (pineapple), and *mangó* (mango). These *pastas* are often served with native *queso blanco* (white cheese). Between-meal eating is quite frequent. Fruits are used at this time and also *café con leche* or some fruit drink. There is a modern trend to use carbonated drinks, which is very unfortunate as their food value is limited to calories.

Use of Vegetables and Fruits

One very weak point in our food habits is the little use made of succulent vegetables. Greens are hardly used and there is a preference for beets, eggplant (*chayote*), for example, which are among the less nutritious ones. The better ones, such as okra, green beans, tomatoes, and carrots, are used in small amounts. Intensive educational programs are trying to make the people conscious of the high nutritional value of the greens and all supermarkets are now carrying them. Only spinach and chard are seen in the regular markets but are not available daily.

Of the yellow vegetables, squash or *calabaza* is very much used, but in small amounts, for example in the preparation of soups and for stews. Everyone likes it made into fritters and into a delicious dessert called *cazuela*. The yellow sweet potato is not used very much. The whitish one is preferred because it is eaten with codfish and being less sweet is a better accompaniment for it.

Of fruits we have plenty and they are of the highest nutritional value. Here is the home of the *acerola* (West Indian or Barbados cherry), which is the highest known food source of as-

TABLE II

Typical Diet That May Be Served to Puerto Ricans Living in the U. S. A.*

Foods	Amount *g*	Calories	Protein *g*	Ca *mg*	Fe *mg*	Vitamins				
						A *i.u.*	Thiamine *mg*	Riboflavin *mg*	Niacin *mg*	Ascorbic acid *mg*
Milk (boiled)	488	330	17	575	0.5	780	0.19	0.83	0.50	—
Meat, round	50	91	9	5	1.4	—	0.04	0.08	2.40	—
Potatoes	120	100	2	13	0.8	24	0.13	0.05	1.40	18
Tomato	50	10	1	6	0.3	550	0.03	0.02	0.25	12
Lettuce	10	2	—	6	0.1	162	—	0.01	0.02	1
String beans	50	17	1	33	0.5	315	0.04	0.05	0.25	5
Sweet pot. (yams)	100	123	2	30	0.7	7,700	0.09	0.05	0.60	20
Rice, enriched	168	600	12	4	4.9	—	0.74	0.05	5.90	—
Beans, red kidney	80	268	18	130	5.5	—	0.46	0.18	2.00	—
Bread, enriched	60	160	5	14	1.1	—	0.15	0.09	1.30	—
Oatmeal	25	98	3	13	1.1	—	0.15	0.04	0.25	—
Orange	150	68	1	50	0.6	280	0.12	0.04	0.30	76
Total		1,867	71	879	17.5	9,810	2.13	1.49	15.17	132
N.R.C. (woman)		2,100†	55	800	12	5,000	1.2	1.4	12	70

* Food values are based on *Composition of Foods—Raw, Processed, Prepared*, Agriculture Handbook, No. 8, Bureau of Human Nutrition and Home Economics, Washington, D. C., 1950.

† This amount is obtained after deducting the 8 per cent recommended by the N.R.C. for Puerto Rico. Calories may be completed with the addition of sugar and fats.

corbic acid. Conservative estimates give 1,000 or more milligrams per 100-gram portion. It is very tiny and looks like a miniature apple, but is sour. We grow oranges which are very juicy and tasty as well as pineapples, grapefruit, papaya, and mango. We have many others generally unknown in the United States and most have proven to be very good sources of vitamin C.

The tropical fruits are the highest in vitamin C. Up to a few years ago the orange and grapefruit were hailed as the best sources of ascorbic acid. It is true that they are high in vitamin C, for one medium-size fruit will furnish the 70 to 75 milligrams that are recommended per day. However, this amount will be furnished by average or even smaller servings of other tropical fruits; for example:

One average serving of papaya
One or two mangos
Two or three slices of fresh pineapple
One or two West Indian cherries (7 grams)
One medium guava
One medium cashew nut fruit.

In Puerto Rico fruit is mainly eaten between meals. Those in the higher socioeconomic strata are more and more including fruit as part of the regular meals. Fruit juices mixed with water and sugar generally are used to quench thirst in the middle of the afternoon. If people serve fruit for dessert, they often choose the imported ones as pears, apple, grapes, which in vitamin content are inferior to tropical ones.

Foods for the Holidays

During religious festivities, especially at Christmastime, a good table is prepared in almost every home. Even the very poor enjoy some of the special dishes of the season.

The most prized one is *lechón asado*. This is a young pig roasted slowly on a spit over an open fire. The animal's vital organs are chopped and stewed into *gandinga*. From the blood, highly seasoned blood sausage is made. This, as well as the roasted meat, is accompanied by boiled (or baked in ashes) green bananas or green plantains. Rice is eaten along with it, either as *arroz blanco* or *arroz con gandules* or *arroz con pollo*. A salad may or may not be added, but another dish called *pasteles* is an indispensable part of the menu. They are made by grating green bananas or green plantains and *yautías* into a sort of dough to which lard colored with annato seeds is added. This dough is spread thin over a banana leaf, a stuffing made of minced pork. *Sofrito*, olives, raisins, and boiled chick peas are put over it and the whole is shaped into a rectangle, tied and boiled.

Typical desserts for such occasions are *dulce de lechosa* (green papaya cooked in syrup); *cazuela; arroz con dulce* (rice cooked with spices and sugar and many times with coconut milk); *almo jábanas* (rice flour and cheese made into fritters); and *manjar blanco* which is a sort of blanc mange made from rice flour,

TABLE III

Additions for Meal Exchange Lists*

Vianda exchanges for diabetics as used at the Veterans Hospital

List No. 2, vegetables, Group A

Add	
Chayote	

List No. 3, fruits

Add		
Guava	3 medium	
Papaya	1/3 medium	
Nispero	1 medium	
Jobo de la India	1 medium	
Acerola	10 large	
Mamey	1/4 cup	

List No. 4, bread and starchy foods

Add		*grams*
Garbanzos or gandules	1/2 cup	
Sweet potato	1 slice—1 1/2 in. x 2 in. diameter or 1/4 cup mashed	60
Ñame cocido	1 slice—1/2 in. x 3 in. diameter or 1/4 cup mashed	60
Green plantain	1/4 medium plátano	40
Ripe plantain	1/3 medium	approx. 50
Tanier	1 small—2 1/2 in. long x 2 in. diameter or 1/4 cup mashed	50
Breadfruit	1/4 cup	50
Apio	1/3 cup mashed or cubed	70

* Meal Exchange Lists, The American Dietetic Association, Chicago.

milk, and sugar flavored with lemon rind or orange leaves.

Fruits and nuts are also served when income permits. They are all imported—English walnuts, filberts, dry figs, dates and raisins and Spanish nougat and other *turrones* made of nuts, almonds, and the like. All this makes a tremendous meal, hard to digest, so everyone will take some alcoholic drink. The preferred drinks are sweet Spanish wine, Puerto Rican rum, light beer and brandy.

Modifications for Therapeutic Diets

Even for diets where carbohydrates must be low some *viandas* may be included. The dietitians at our Veterans Hospital have added exchanges to the Diabetic Exchange Lists prepared in the States. The patients are highly pleased to be able to select some of their well-liked foods (see Table III).

For low-sodium diets the *viandas* that are acceptable to the patients are ripe plantain, green plantain (if baked), pumpkin, and baked sweet potato. *Arroz con pollo* is a dish well liked without salt. A sort of sauce called *ajilimójili* when added to unsalted *viandas* makes them very palatable. It is prepared by adding chopped green peppers to vinegar and oil, *aji dulce* (sweet chili pepper), raw onions, and a tiny amount of garlic. When allowed to stand for one or more days, the flavor improves. The sodium content of *viandas* is not yet known, but analyses are being made by the research department of the Veteran's Hospital. *Viandas* are a boon to low-fat diets. When used as an accompaniment for stewed meat, codfish or salmon,

GLOSSARY OF TERMS

Achiote (Annato)	Yellow coloring used with rice
Ajilimójili	Sauce made of oil and vinegar and seasonings
Aji dulce	Sweet chili pepper
Almojábanas	Fritters of rice flour and cheese
Arroz blanco	White rice cooked in water with lard and salt
Arroz con dulce	Dessert made of rice with sugar and spices and coconut milk
Arroz con habichuelas	Rice stewed with beans and sofrito
Arroz con pollo	Dish of rice with chicken, olives, Spanish red pepper and sofrito
Asopao	Thick soup of chicken and rice
Avellanas	Filberts
Bacalao	Dried, salted codfish
Batata	White or yellow sweet potato
Café con leche	Black coffee and milk
Calabaza	A cross between squash and pumpkin
Cazuela	Dessert made of grayish-white sweet potato and calabaza with eggs, butter, sugar, spices, cows milk, or coconut milk
Dulce de lechosa	Green papaya cooked in syrup
Gandinga	Stew of liver and other organs
Gandules	Pigeon peas
Granos	Local name for dry legumes
Habichuelas guisadas	Stew beans made with sofrito
Leche de coco	Coconut milk made from grated fully mature coconuts
Lechón asado	Roasted pig over open fire
Manjar blanco	Dessert made of rice, flour, milk, sugar, and flavoring
Morcilla	Blood sausage
Ñame	One of the viandas
Naranja	Bitter orange
Panapén	Breadfruit
Pasteles	Dish made of grated viandas with meat stuffing and boiled in banana leaves
Pasta de grayaba	Guava paste
Piña	Pineapple
Plantain	Starchy banana
Queso blanco	White Puerto Rican cheese
Recao	Seasoning herbs
Sancocho	Stew made from viandas and meat
Serenata	Dish of boiled viandas, dry codfish and served with oil, etc.
Sofrito	Sauce made sautéing tomato (or tomato sauce), onion, garlic, smoked ham, and green pepper in fat. Used as the basis of Puerto Rican cooking
Sopón	Sort of stew made with meat, or codfish, or legumes and rice
Tinta de café	Coffee extract
Turrón alicante	Spanish nougat
Viandas	Starch vegetables like green bananas, taniers, etc.
Yautía	A vianda
Yuca	A vianda

the patients relish them. *Ñame, yautía,* and *plátano amarillo* are the best for this purpose. They are preferred to potato. Patients with ulcer like cream of *yautía* or *calabaza* soup very much, and mashed *ñame* and *yautías* are better liked than mashed potato. This is especially true if the patients come from the low-income or rural groups.

In the dietetic treatment of tropical sprue, research workers in Puerto Rico have observed that potato starch is not tolerated but green and ripe plantain, green bananas, *yautías,* and *ñame* are, regardless of the fact that they have a higher carbohydrate content (19 per cent for potatoes and from 25 to 39.8 per cent for the others). No scientific explanation for this difference has yet been found.

It is realized that most dietitians in the United States will be unable to feed *viandas* to their patients, but those who work with Puerto Rican groups in New York City, Miami, Philadelphia, and other big centers will find them in the Puerto Rican markets. Florida grows many of the same fruits and vegetables we grow in Puerto Rico, and with all the modern facilities for the marketing of fresh products as well as for quick transportation it is not unreasonable to hope that *viandas* as well as tropical fruits will soon be available to dietitians everywhere.

ACKNOWLEDGMENT

The author wishes to thank Dr. Lydia J. Roberts for her helpful suggestions and comments.

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Nutrition News

Gordon Research Conference on Food and Nutrition

The Gordon Research Conference on Food and Nutrition for 1959 will be held August 17–21 at Colby Junior College, New London, New Hampshire.

Attendance at the Conference is by application. Application should be made to the Director at least two months before the date of the Conference, and *must be submitted on the form* which may be obtained by writing the office of the Director.

The fixed fee of $100.00 for attendance at the Conference includes registration and room and meals.

The program for the five-day conference is as follows:

GORDON RESEARCH CONFERENCE ON FOOD AND NUTRITION

L. J. TEPLY, *Chairman*
D. B. HAND, *Vice Chairman*

August 17 C. A. BAUMANN and E. E. HOWE, *Chairmen*
Some Vitamin-Carbohydrate Interrelationships. JOHN YUDKIN.
Nutritional Aspects of Saturated Fats. D. C. HERTING.
Clinical and Practical Aspects of Protein Malnutrition. M. BÉHAR.

August 18
H. P. BROQUIST and R. A. HARTE, *Chairmen*
Human Requirements for Some of the "Lesser" B-Vitamins. W. J. DARBY.
Metabolism of Nucleic Acids in Normal and Pathological Thyroid. J. MATOVINOVIC.
What Is a Normal, Acceptable, or Desirable State of Nutrition. *Panel:* GRACE A. GOLDSMITH, F. J. STARE, W. A. KREHL, J. M. BROŽEK.

August 19
HARTLEY HOWARD and R. H. SILBER, *Chairmen*
Food Standards and the Public Welfare. P. L. DAY.
Nutrition Education and Nutritional Advertising. P. L. WHITE.
Metabolic Functions of Vitamin E and Ubiquinone. R. E. OLSON.
Discussion: M. K. HORWITT.

August 20
A. E. SCHAEFER and Z. I. KERTESZ, *Chairmen*
Relationship of Food to Radiation Effects. H. SPECTOR.
Unidentified Factors in Chick Nutrition. J. R. COUCH.
Problems and Possibilities in Improving Indigenous Foods. A. G. VAN VEEN.

August 21 D. B. HAND, *Chairman*
Ascorbic Acid in Food Technology. J. C. BAUERNFEIND.
The Future of Pressurized Food Packages. F. W. BLODGETT.

Gordon Research Conferences in other fields will be held from June 15–September 4.

Requests for attendance at this conference, or for additional information, should be addressed to W. GEORGE PARKS, Director, Department of Chemistry, University of Rhode Island, Kingston, R. I. After June 15, mail should be sent to Colby Junior College, New London, N. H.

American Dietetic Association

The American Dietetic Association will hold its forty-second annual meeting August 25 through 28, 1959, at Los Angeles, California. Sessions and exhibits are scheduled for the Shrine Convention Hall and Auditorium. The headquarters hotel will be the Statler Hilton.

Community Nutrition Institute of Syracuse University

The College of Home Economics, Syracuse University, and the Nutrition Bureau, New York State Department of Health, are sponsoring the thirteenth consecutive Community Nutrition Institute at Syracuse University, June 15–26, 1959.

The first week will present in retrospect the development of our knowledge of nutrition during the early part of the twentieth century and a review of our past and present knowledge of the recommended dietary allowances, mineral

and trace element metabolism, lipid metabolism, and food practices of the American public. During the second week a clinician, epidemiologist, statistician, anthropologist, and nutritionist will discuss the methods used and problems involved in designing a study, collecting and analyzing data, and applying the results. Martha F. Trulson, D.SC., Department of Nutrition, School of Public Health, Harvard University, will direct the program for this second week.

For further information write Dr. Anne Bourquin, Department of Foods and Nutrition, College of Home Economics, Syracuse University, Syracuse 10, N. Y.

Council on Arteriosclerosis

The Council on Arteriosclerosis of the American Heart Association–American Society for the Study of Arteriosclerosis will hold its Thirteenth Annual Meeting on November 8 and 9, 1959, at the Hotel Knickerbocker, Chicago, Illinois. Physicians wishing to present papers at this meeting should send factual abstracts of their presentations before June 12, 1959, to Dr. A. Kellner, 525 East 68th Street, New York 21, N. Y.

Sixth International Congress for Internal Medicine

The Sixth International Congress for Internal Medicine will be held in Basel, Switzerland, August 24–27, 1960. This Congress will be organized in conjunction with the Swiss Society for Internal Medicine. For further details apply to the Secretariat of the Sixth International Congress for Internal Medicine, 13, Steinentorstr., Basel.

Reviews of Recent Books

Metabolism of Lipids. *British Medical Bulletin*, vol. 14, No. 3, September, 1958. The British Council, London, pp. 197–278, $3.25.

Rapid progress in a field—or at any rate, rapid accumulation of data—calls for a symposium. *Metabolism of Lipids*, which is the subject of the symposium reported in a recent issue of *British Medical Bulletin*, stands especially in need of review, since in recent years the volume of research activity has risen sharply under the stimuli of new techniques and abundant money given to fight arteriosclerosis.

The papers deal with a wide range of topics. For the chemists there are detailed and rather specialized accounts of current work on some aspects of lipogenesis; for the physiologist, discussions of fat absorption and transport and of hormonal control. Clinicians will find a number of sections of practical interest, notably Frazer's discussion of steatorrhea in relation to gluten sensitivity, and the papers on essential fatty acid deficiency by James and Lovelock, and by Sinclair.

Bronte-Stewart's discussion of diet, blood lipid, and heart disease makes the important point (sometimes ignored by clinical enthusiasts) that all the well-controlled clinical studies to date have been concerned with the relation between diet and concentration of blood lipid. As a result of much work in different laboratories it is now clearly established that the composition and amount of dietary fat can influence the concentration of various lipid fractions in the blood. It is tempting to proceed from this result to the conclusion that dietary fat causes coronary artery disease. Epidemiologic studies and animal work do give indirect support to this hypothesis, but the practical nutritionist must remember that the link between diet and disease is at present a working hypothesis, "founded more on assumption than on fact" (p. 251). All will agree with the further conclusion that the problem is of capital importance, deserving vigorous study.

The chief limitations of the symposium are simply those inherent in any meeting in which active investigators report on their own fields of interest. Such a collection of papers does not provide anything like a comprehensive review of the various topics listed, and in some cases the reports fail to give enough background material to make them accessible to the non-expert. But these, after all, are the objectives of textbooks and other kinds of general review. Those of us—chemist, physiologist, and clinician—who are concerned with some aspect of this large subject, and who look with dismay at the volume of periodical literature, will profit from the issue and be grateful to the distinguished contributors for sharing with us their working hypothesis.

VINCENT P. DOLE

Advances in Clinical Chemistry, vol. 1, edited by H. Sobotka and C. P. Stewart. Academic Press Inc., New York, 1958, pp. 398, $12.00.

Here is a book that will be welcomed by clinical chemists, clinicians, and workers in related fields. The aim in this "Advances" series is to produce readable accounts of selected important developments, of their roots in the allied fundamental disciplines, and of their impact upon the progress of medical science. The articles are written by experts who are actually working in the field they describe. This is not merely a methods book. The various methods are critically presented, the details being fully discussed. In addition to the clinical application, interpretation of the methods is provided, and the metabolic and pathologic aspects of the subjects are expertly reviewed. The bibliography appended to each chapter not only serves to document the author's statements but also refers the reader to original publications for full details or other viewpoints and opinions.

In Volume 1 the subjects presented are plasma iron, the assessment of the tubular function of the kidneys, protein-bound iodine, blood plasma levels of radioactive iodine-131 in the diagnosis of hyperthyroidism, determination of individual adrenocortical steroids, the 5-hydroxyindoles, paper electrophoresis of proteins and protein-bound substances in clinical investigations, composition of the body fluids in childhood, and the clinical significance of alterations in transaminase activities of serum and other body fluids.

O. M. HELMER

Care of the Premature Infant, by Evelyn C. Lundeen and Ralph H. Kundstadter. J. B. Lippincott Company, Philadelphia, 1958, pp. 367, $8.00.

This book serves essentially as a nursing text with a synoptic review of medical aspects in the care of the premature infant. It represents a modest revision of *The Premature Infant* by Julius H. Hess, M.D., and Miss Lundeen, published in 1949.

Although rich in valuable practical detail and reported experience, this book contains much that is archaic, ritualistic, and tradition-bound, and is therefore somewhat disappointing as a text for medical students or physicians. From the point of view of

nurses with special interest in the premature infant, the book contains excellent descriptions in exact and extensive detail of nursing routines, technique, and procedures used at the Hortense Schoen Joseph Premature Infant Station at Michael Reese Hospital, Chicago. Equipment, organization, and administration of the nursery staff and teaching curriculum, records, follow-up care, etc., are thoroughly covered. Principles of feeding and feeding techniques are well described, particularly in regard to the use of breast milk.

The chapter on therapeutic procedures covers a variety of subjects. The potential toxicity of oxygen is inadequately emphasized, although mention is made of monitoring oxygen saturation in incubators. Recent improvements in intravenous technique, such as the use of the Gardner-Murphy needle, are not included, although the use of the mustard bath is described. The method described for artificial respiration is specifically discouraged by Committee on the Fetus and Newborn of the American Academy of Pediatrics.

The discussion of use of antibiotics is a new chapter and consists of a review of the preparations available. Throughout the book, the problem of staphylococcal and *E. coli* infections is barely, and indirectly, touched upon. The use of aseptic technique receives excellent description and emphasis, however.

The section "Pathologic Conditions and Their Management" is quite inclusive in scope. Although the subject of erythroblastosis fetalis is discussed in detail, virtually nothing is said of the special problems which attend the premature infant with this disorder. Liver extract is recommended in the treatment of anemia. The management of diarrhea is described in general terms.

Perhaps the best features of the book are the excellent descriptions of the home and follow-up care programs. The team and community approach to the total premature care are emphasized and detailed, including the Chicago Plan.

The statistical analyses provide valuable information. Of particular interest is a developmental follow-up study of premature infants whose birth weights were 1250 g or less, with special reference to those who have attained age 18 years or older. T. C. PANOS

Vitamins and Hormones: Advances in Research and Applications, Volume XVI, edited by Robert S. Harris, G. F. Harrison, and Kenneth V. Thimann. Academic Press Inc., New York, 1958, pp. 374, $11.60.

The sixteenth annual volume of this series of reviews contains the high quality readers have learned to expect. Nutrition is well represented by Geiman's "Nutritional Effects of Parasitic Infections and Disease," Lutwak-Mann's "Dependence of Gonadal Function upon Vitamins and Other Nutritional Factors," and Snell's "Chemical Structure in Relation to Biological Activities of Vitamin B_6." Hormonal aspects of coronary artery disease, the physiology of secretion, and the chemistry and physiology of thyroid-stimulating hormone and synthetic derivatives of corticoids are also discussed. A particular valuable article is Behrens and Bromer's review of glucagon.

Special mention should be made of the article by Felch, Sinisterra, VanItallie, and Stare on vitamins and other nutrients in cardiovascular disease. These authors take the stand that the popular epidemiologic "evidence" linking total fat intake to atherosclerosis is inadequate. In addition they believe that the concept of fatty acid imbalance producing hypercholesteremia has not been shown to be applicable to "conditions of ordinary everyday life." Most workers will agree with them that the relationship between hypercholesteremia and human atherosclerosis has not been conclusively proved to be one of cause and effect. This review of a vital subject is a well-balanced critical appraisal of a field in which feelings are strong but evidence weak.

Again, the reader should thank the authors and editors for their service in preparing these lucid and useful reviews. S. O. W.

Essential Fatty Acids, edited by H. M. Sinclair. Academic Press Inc., New York, 1958, pp. 268, $9.50.

This book is the Proceedings of the Fourth International Conference on Biochemical Problems of Lipids. It has the familiar advantages and disadvantages of this kind of publication. It has been well edited. The papers are succinctly given and the transcripts of the discussions in most places have been cut to reasonable size and germane topics. A total of 37 papers are included, covering recent work in the chemical aspects, absorption and distribution, and biochemical functions of fatty acids. The concluding section is a general discussion of essential fatty acids.

The papers vary considerably in the detail with which they are presented, extent of discussion, completeness of coverage, etc. The principal value of the book is that it provides a rather broad coverage of recent research activities and advances in the broad field of the chemistry and metabolism of fats with emphasis upon essential fatty acids and atherosclerosis. Those who are primarily clinicians or biochemists will probably learn most from the reports of the chemists and vice versa. The title should not lead one to believe, of course, that this is a monograph on the essential fatty acids. D. MARK HEGSTED

Remedies and Rackets: The Truth about Patent Medicines Today, by James Cook. W. W. Norton & Company, Inc., New York, 1958, pp. 237, $3.75.

This "exposé" was written by a newspaper man and is said to be "essentially a book of facts" with much of its substance drawn from documents of the Food and Drug Administration, Post Office Department Fraud Division, F. T. C., etc. Be that as it may, the book is an obvious attempt at sensationalism. Titles such as "Vitamins and Voodoo" and "The Truth about Drug Prices" will indicate the razzle-dazzle approach. Much is left unsaid or is implied by innuendo. This is re-

flected in the author's attack against reputable pharmaceutical companies. He is on safer ground when he attacks the rejuvenating quackeries, the nonsensical nostrums, and the false claims of so-called reducing remedies. It is unfortunate that the author could not distinguish between the true, the half-true, and the untrue. The book cannot be recommended.

S. O. W.

Nutrition and Diet Therapy for Practical Nurses, by Lillian Mowry. C. V. Mosby Company, St. Louis, 1958, pp. 165, $2.50.

The author of this little book is a hospital dietitian, who is aware of the type of questions which practical nurses are asked concerning food. The book is an effort to present, in understandable language, the knowledge of nutrition and diet therapy in relation to the total care of the patient.

The book is divided into two sections. Chapter 1 in the first section explains the importance of a balanced diet. The following chapters discuss carbohydrates, protein, fat, energy requirements, minerals and vitamins, digestion, planning menus for the family, and sanitation. The use of the basic four in translating the recommended allowances over into the daily needs brings the book up to date.

The second section, covering diet therapy, may easily be understood by a practical nurse. An attempt is made to simplify all terminology. This section if well covered by the instructor should give the student an appreciation of the importance of diet restrictions ordered by the physician. The diet for the diabetic is simplified by the use of exchanges. With good instruction the student should be able to calculate and manage the diet with confidence. Low-sodium diets, which are so often mismanaged from lack of understanding and confusion because of terminology, are carefully outlined to include the various levels of sodium intake. This is done very simply and should be followed with ease by the student.

Other chapters include routine hospital diets, modifications in individual constituents such as high caloric diets, high-protein, low-protein, low-fat, and minimum-fat diets, obesity, underweight, modifications in consistency, as diets in ulcer management, and allergy.

Long tables of food values have been omitted and in their place a valuable list of common foods are given in their household measures with their corresponding caloric value. A very valuable glossary of terms used in nutrition and diet therapy is given at the end of the book.

The reviewer believes that the value of the book will depend on the ability of the instructor who uses it. The suggestions for additional study given at the end of every chapter are excellent, and if used should stimulate the interest of the nurse. References used are from reliable sources. More emphasis could have been given to the description of the regular soft, mechanical soft, medical liquid, and surgical liquid diets (p. 89). The answers to some of the questions at the end of that chapter can only be found by referring to the references listed.

The author has done well in gathering a great deal of information together in a small, easily read book without sacrificing important things. It comes at a time when there is a great need for this book.

SR. MAUDE BEHRMAN

BOOKS RECEIVED

Books received for review by THE AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Eat Well and Stay Well, by Ancel and Margaret Keys, Doubleday & Company, Inc., New York, 1959, pp. 359, $3.95.

Shaker Recipes for Cooks and Homemakers, by William Lawrence Lassiter, Greenwich Book Publishers, New York, 1959, pp. 302, $4.50.

Diseases of Laboratory Primates, by Theodore C. Ruch, W. B. Saunders Company, Philadelphia, 1959, pp. 600, $7.50.

Gift Book of Personal Ideas, by Mary Mountain Scott, Greenwich Book Publishers, New York, 1959, pp. 39, $2.50.

Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, edited by Garfield G. Duncan, W. B. Saunders Company, Philadelphia, 1959, pp. 1104, $18.50.

Overfed but Undernourished: Nutritional Aspects of Health and Disease, by H. Curtis Wood, Jr., Exposition Press, New York, 1959, pp. 95, $2.50.

Ciba Foundation Symposium on Biosynthesis of Terpenes and Sterols, edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, Little, Brown & Company, Boston, 1959, pp. 311, $8.75.

Abstracts of Current Literature

OBESITY: CLINICAL AND EXPERIMENTAL DATA

A vast array of weight-reduction programs has been displayed to the public in the lay press and to physicians in the medical literature. Diets have been advocated which provide high-protein high-fat, or high-carbohydrate content with caloric limitations, each devised to promote satiety or to inhibit the hypothalamic centers for appetite control. The abstracts following exemplify the wide range of programs utilized by various investigators.

A Weight-Reducing Experiment. M. A. Harris and G. H. Roehm. *J. Am. Dietet. Assoc.* 33: 1255, 1957.

Ten freshman women at Montana State College responded favorably to a weight-reducing program which called for eating lightly of "starchy and fatty" foods, taking second helpings of salads or vegetables when allowed, eating all the meats or protein foods, and eliminating desserts. These students lived in one residence hall and ate at the regular dining table. Special diets were not served and calories were not counted. At the beginning of the study the ten girls were 14 to 54 pounds over their ideal weight as determined by standards of Justin, Rust, and Vail. During the first three months, the average weight loss was 6.25 lb per person for the diet squad in comparison with an average gain of 2.3 lb for the other dormitory residents. The nutrition instruction was given weekly for 10 weeks according to a plan previously described (*J. Home Econ.* 49: 419, 1957). At the end of the six-month experimental period there was an average weight loss of 6.3 lb per girl. The authors believe this failure to show additional weight loss indicates that the girls needed closer supervision for a longer period of time in order to help them change their pattern of eating.

Serum cholesterol values and basal metabolic rate determinations at the beginning, mid-point, and end of the study failed to show significant changes. The authors conclude that this sort of dietary regimen had no significant influence on these biochemical values for any of the subjects.

The educational plan appears to have considerable merit when one notes the losses of the ten girls in comparison to the average weight gains in the remainder of the residents.

J. M. SMITH

The Use of a Formula Diet for Weight Reduction of Obese Out-Patients. A. R. Fernstein, V. P. Dole, and I. L. Schwartz. *Ann. Int. Med.* 48: 330, 1958.

The use of formula diets in the accomplishment of metabolic studies has been popular for many years. The authors applied such a diet to a group of 106 obese outpatients in an effort to effect weight reduction. The diet consisted of 22 g of protein (evaporated milk), 52 g of fat (corn oil), and 85 of carbohydrate (dextrose) in 8 oz of water. It supplied 896 calories per day and was supplemented with vitamins, extra water, black coffee or tea, noncaloric sweeteners, unflavored carbonated water, and low-calorie soda beverages. The formula was divided into five or six daily feedings.

Fifty-three per cent of those who began treatment lost over 20 lb; 28 per cent lost over 40 lb. Following the discontinuation of the formula 46 per cent of the subjects who had lost 30 lb or more had been able to limit their weight regain to less than 30 per cent of the original loss. It was concluded by the authors in comparison to other methods that formula feeding can be a useful adjunct of a weight-reduction program.

J. F. MUELLER

Treating Overweight Patients. G. L. Thorpe. *J.A.M.A.* 165: 1361, 1957.

The author claims that the diet which will produce the most rapid loss of weight without hunger, weakness, or lethargy is made up chiefly of meat, fat, and water. This is a high-protein, high-fat, low-carbohydrate diet. According to this opinion, the total quantity eaten need not be noted, but the ratio of three parts of lean to one part of fat must be maintained. The usual makeup of such a diet is 6 ounces of lean meat and 2 ounces of fat three times daily. After two to four weeks, the patient is given 3 per cent and 5 per cent carbohydrate fruits and vegetables. The over-all weight loss is said to be approximately $1^1/_2$ pounds per week. There are a number of other specific recommendations made in the article.

No new data are presented or any figures given for the actual experience among patients. This could have been the result of the fact that the paper was an address, given by the chairman of the section on general practice of the American Medical Association. The paper raises a large number of questions, and the reader would certainly want to question some of the assumptions made on the basis of a highly selective review of the complex literature on obesity. S. O. Waife

The response of the individual to weight reduction is unpredictable. Some will feel improved and derive a sense of physical and emotional well-being from the process; others become emotionally distressed, irritable, and subject to fatigue and lethargy. While psychologic factors may be important in these responses, it is important that we increase our knowledge of metabolic transformations occurring during the course of weight loss by intensive dieting.

Weight Reduction in Obese Young Men. C. M. Young, E. I. Empey, V. U. Serraon, and Z. H. Pierce. *J. Nutrition* 61: 437, 1957.

A number of workers have reported metabolic studies of obese young women during weight reduction by controlled feeding. Regardless of the type of diet used, in most instances calcium, nitrogen, and phosphorus retention was less satisfactory during weight reduction than in nonobese women of comparable age or with the same obese subjects in the prereduction period. Furthermore, there was a tendency for retention to diminish as the periods of weight reduction were prolonged. No adequate explanations have been advanced for the poor calcium retention.

Nitrogen, calcium, and phosphorus metabolism, on a constant intake of the three nutrients, was studied in 8 obese young men by means of seven-day balance studies in a prereduction period of weight maintenance, at the fourth and eighth weeks of weight reduction, and at the fourth week of postreduction weight maintenance. Weight losses in the 8-week reduction period ranged from 13.4 to 27.5 lb, with a mean of 22.6 and a median of 23.6 lb.

Four of the 8 subjects went from nitrogen and phosphorus retention or equilibrium in the prereduction period to nitrogen and phosphorus loss during the period of caloric restriction. Within the limits of the experiment the losses did not appear to increase with prolongation of the reduction period. Relief of caloric restriction was accompanied by return to equilibrium or retention with respect to these nutrients but at a lower level. In contrast to women subjects studied previously, only 3 of the 8 men went into calcium deficit, and the deficit occurred early in the weight-reduction period, with subsequent return to calcium equilibrium in the later stages of reduction. No satisfactory explanation is given for the changes in calcium retention; they are discussed in terms of the emotional stability and relative rate of weight loss in the subjects. In 7 of the 8 subjects 24-hour basal caloric requirements decreased during weight reduction; the mean decrease was 150 calories, or 8.4 per cent. B. Sure

The Chemical Composition of the Tissue Lost by Obese Patients on a Reducing Regimen. R. Passmore, J. A. Strong, and F. J. Ritchie. *Brit. J. Nutrition* 12: 113, 1958.

By studying nitrogen balances, the daily energy intake and output, and metabolic rates, the authors have calculated the composition of obesity tissue lost by seven patients during a six-week period of weight reduction. In the first few days there was a loss of 2–4 l of body water, possibly due to the change to a low-carbohydrate diet. This was followed by a period of water retention, somewhat analogous to "hunger edema." During the whole period, fat accounted for 73–83 per cent of the weight lost, protein formed 4–7 per cent, and the remaining 10–23 per cent was attributed to water loss. W. H. J. Summerskill

Clinical Observations on Obese Patients during a Strict Reducing Regimen. J. A. Strong, R. Passmore, and F. J. Ritchie. *Brit. J. Nutrition* 12: 105, 1958.

In addition to a strict diet supplying 400 calories per day, the authors emphasize the contribution of regular exercise to weight reduction and encouraged a three to four hour daily walk. Seven patients were treated on this regimen for six weeks, during which time each lost 13–16 kg, with daily negative energy balances sometimes amounting to 3,100 calories. Good health was maintained, and hunger was not excessive. Ketosis under such circumstances is less liable to occur in obese subjects and, although found in three patients, it was only moderate and in no way affected their activities. W. H. J. Summerskill

Individuals who stop smoking will generally "take a snack instead of a smoke." This situation frequently complicates the management of the obese coronary patient who is instructed to stop smoking at the same time that he is placed on a weight-reduction program.

Changes of Body Weight in Normal Men Who Stop Smoking Cigarettes. J. Brožek and A. Keys. *Science* 125: 1203, 1957.

A statistically significant difference in changes of body weight was found in a group of middle-aged men who had stopped smoking for two years, when compared with a matched control group (smokers). Using the average weights for two years prior and for two years following the voluntary cessation of cigarette smoking, the control group lost 1.1 lb whereas the experimental group gained 8.2 lb. The mechanism for this generally recognized phenomenon is still unknown.

S. O. WAIFE

There have been several reports attacking the thesis that obesity is a deterrent to longevity. It has been suggested that the actuarial data on which this concept is based are not representative of the general population.

Obesity as a Health Factor in Geriatric Patients. J. Pomeranze. *Geriatrics* 12: 481, 1957.

The author attempts to show that obesity is as common in patients over 75 as it is in the general population. Obesity was determined by weight in relation to height, and by the thickness of skin fold measured manually. In a group of 121 patients, 23, or 19.1 per cent, were considered obese.

Total cholesterol, phospholipids, and total lipids were measured in nine obese male subjects. There was no correlation with obesity.

Four case histories are presented as being typical of older patients who have lived to an advanced age despite their handicap of obesity. The author states: "This group of obese geriatic patients tends to discredit the commonly accepted dictum that obese patients do not live to advanced years."

This study is of interest and should be extended to include a larger number of patients, especially as regards lipid metabolism. K. R. CRISPELL

The difficulty in obtaining an accurate sphygmomanometric reading in the obese subject is a phenomenon not appreciated by most physicians.

Overweight and Hypertension. T. Bjerkedal. *Acta med. scandinav.* 159: 13, 1957.

The relationship between overweight and arterial hypertension was assessed from records from industrial plants in over 14,000 individuals.

Higher systolic and diastolic pressures were related to increasing obesity, but the elevation of pressures was small and uniform. In particular, there was no accumulation in this group of patients with severe hypertension. It is argued that these results support earlier work which demonstrated that auscultatory blood pressure readings were higher than intra-arterial measurements in obese subjects, and that the apparent relationship between hypertension and obesity is due solely to this effect of the circumference of the arm on auscultatory blood pressure readings.

W. H. J. SUMMERSKILL

Some of the physiologic and biochemical alterations occurring in mice with hereditary and experimental obesity are described in the following papers.

CO_2 Output and Energy Balance of Hereditary Obese Mice. R. McClintock and N. Lifson. *Am. J. Physiol.* 189: 463, 1957.

The total CO_2 outputs of young adult hereditarily obese-hyperglycemic mice were measured over two-day periods by means of the D_2O^{18} method, and were found to be significantly higher than those of littermate controls. Since it had previously been postulated that the development of obesity in these animals was related in large part to a decreased total energy output, the energy balance of growing obese and normal mice was then studied. Food consumption, weight gains, and total CO_2 outputs were determined at the ages of 6, 9, and 12 weeks. The CO_2 outputs, which reflect the energy outputs, were of approximately the same magnitude for the two groups at 6 and 9 weeks of age, but were greater for the obese at 12 weeks. Food consumption remained nearly constant for both groups. An energy balance from these data is contrasted with one previously postulated by another group for similar mice.

AUTHORS

Measurement of "Basal" and Total Metabolism in Hereditarily Obese-Hyperglycemic Mice. R. McClintock and N. Lifson. *Am. J. Physiol.* 193: 495, 1958.

Measurements of oxygen consumption and CO_2 production were made by the Haldane open-circuit method on hereditarily obese mice and littermate controls, and the energy expenditures were estimated. Studies were made on mice for short periods under "basal" conditions, and for periods of approximately a day with the mice fasted and confined, fasted and relatively unconfined, and fed and unconfined. The total energy expenditures of fed and unconfined obese mice were found to be higher than those of nonobese littermate controls by virtue of (a) increased "basal metabolism," (b) greater energy expenditure associated with feeding, and possibly (c) larger energy output for activity despite reduced voluntary movement. The values obtained for total metabolism confirm those previously determined by an isotope method for measuring CO_2 output.

AUTHORS

Organ Weights in Three Forms of Experimenta Obesity in the Mouse. N. B. Marshall, S. B. Andrus and J. Mayer. *Am. J. Physiol.* 189: 343, 1957.

Obesity in mice is accompanied by changes in organ weight. Certain changes, such as the enlargement of the liver, heart, and kidneys, appear to be nonspecific effects of prolonged hyperphagia. Such changes are seen in "regulatory" as well as in "metabolic" obesities. Other changes may be part of a syndrome of which obesity is also a component; for example, in the hereditary obese-hyperglycemic syndrome, a metabolic form of

obesity, the pancreas and the thymus are enlarged and the size of the brain decreased. These findings emphasize the need for a wider recognition of the differences between obesities of various etiologies and pathogeneses.

AUTHORS

Neuroendocrine System and Obesity Studies in "Yellow" Mice. M. Silberberg and R. Silberberg. *J. Mt. Sinai Hosp. New York* 24: 1207, 1957.

Mice of strain YBR/Wi are represented by two genotypes. One genotype possesses the A^y gene; these animals are yellow-coated and become obese when fed enriched diet. Animals not possessing the A^y gene are gray and do not become obese when fed diets enriched with fat or carbohydrates. Except for coat color and potential obesity the "gray" and "yellow" mice have a similar anatomic and physiologic constitution. No major structural differences were observed in the endocrine organs. Studies of the neuroendocrine system gave the following results: The yellow-coated mice had hypoplastic brains; particularly obvious was hypoplasia of the paraventricular nuclei associated with degeneration of the thalamic, hypothalamic, and cerebellar nuclei and formation of calcified plaques. These lesions represent a major difference between the otherwise phenotypically similar genotypes and are thought to be related to the tendency of the "yellows" to develop obesity.

M. SILBERBERG

Effect of Changes in Ambient Temperature on Spontaneous Activity, Food Intake and Body Weight of Goldthioglucose-Obese and Nonobese Mice. M. J. Fregly, N. B. Marshall, and J. Mayer. *Am. J. Physiol.* 188: 435, 1957.

Goldthioglucose-obese mice cannot adjust their food intake to meet the increased energy requirements due to cold. At all ambient temperatures above 15°C the spontaneous running activity of these animals is less than that observed for nonobese controls. Activity of obese mice is maximal at 19°C and minimal at 15°C or lower. Body weights decrease during exposure to cold. In contrast to that of obese mice, running activity of nonobese controls is maximal at an ambient temperature of 25°C but nearly ceases at 15°C or lower. The food intake of these animals increases in the cold and remains elevated even at temperatures at which activity decreases. The body weight of nonobese controls either remains constant or increases during exposure to cold air.

AUTHORS

Effects of Exposure of Obese Rats to Simulated High Altitudes. P. D. Altland, O. Michelsen, and B. Highman. *Am. J. Physiol.* 191: 371, 1957.

Osborne-Mendel rats became obese when fed a high-fat diet for 6 to 15 monhts. Obese rats and stock-fed rats were exposed six and one-half hours a day, five days a week to 18,000 or 25,000 feet simulated altitude for from four to six months. Both groups of rats developed the same degree of polycythemia and had the same mortality rate. The obese rats lost more weight from altitude exposure and also showed a slightly higher incidence of cardiovalvular thickening and cardiac vegetations, particularly among those that died. The mean heart weight of unexposed obese rats was 50 per cent greater than that of stock-fed rats; the heart weights of both groups increased about 70 per cent following 191 days of exposure. In acute altitude tests at 33,500 feet simulated altitude, both Osborne-Mendel and Sprague-Dawley rats on the high-fat diet, irrespective of the degree of obesity, died within 86 minutes; 60 per cent of the stock-fed rats survived for a longer period. Some of the heaviest Osborne-Mendel rats on the high-fat diet died within three minutes at this altitude. Preoxygenation prevented these early deaths, but neither preoxygenation nor a slow rate of ascent (500 ft/min) had any effect on the high mortality of rats on a high-fat diet exposed to altitude.

AUTHORS

THIAMINE DEFICIENCY

The prime function of thiamine is its role in pyruvate metabolism. The phosphorylated thiamine acts as a coenzyme for carboxylase, the enzyme which catalyzes the decarboxylation of pyruvate to acetate and carbon dioxide. In thiamine-deficiency states there is an accumulation of pyruvic and lactic acid. The thiamine-sparing action of fat and protein is well known and is attributed to the substitution of substrate other than glucose from which pyruvate is derived. Sorbitol is utilized ultimately as fructose and glucose through metabolic conversions. The sparing action of sorbitol upon thiamine requirements must be found in some mechanism other than reduced pyruvate formation.

The Vitamin Sparing Action of Sorbitol. T. B. Morgan and J. Yudkin. *Nature, London* 180: 543, 1957.

Professor Yudkin has already shown that despite the absence of dietary thiamine rats can survive for many months if carbohydrate is also excluded from the diet. Polyneuritis and death follow the addition to the diet of as little as 5 per cent carbohydrate.

In the present study, animals survived and gained weight on a thiamine-free diet containing as much as 20 per cent carbohydrate provided that sorbitol was given simultaneously. The tissues of these rats contained more thiamine than those of the control animals, and the protective action of sorbitol was attributed to an alteration of the intestinal flora which encouraged thiamine synthesis. Sorbitol produced diarrhea, with enlargement of the cecum and an increase in its fecal content. Subsequent experiments showed that sorbitol made animals independent of dietary sources of the other B vitamins as well as thiamine.

Whether sorbitol would have a similar action on human thiamine requirements is an interesting possibility which might be investigated, for example, in patients with Wernicke's encephalopathy.

W. H. J. SUMMERSKILL

The use of methylene blue to produce changes in the rate of glucose oxidation provides a means for detecting thiamine deficiency. Evidence is presented below indicating that in this deficiency there is not only a reduction in the rate of glycolysis but also a change in the oxidative pathway.

The Effect of Thiamine Deficiency on the Glucose Oxidative Pathway of Rat Erythrocytes. M. Brin, S. S. Shohet, and C. S. Davidson. *J. Biol. Chem.* 230: 319, 1958.

Removal of thiamine from the diet of rats resulted in a depression of the glucose monophosphate oxidative shunt of the erythrocytes at the step of transketolation from pentose to heptulose. Rats were kept on a thiamine-depleted diet up to 58 days. Erythrocytes obtained at intervals and incubated with 100 mg/per 100 ml glucose at pH 7.4 in the presence of 3.5 mg/100 ml methylene blue showed increasing pentose and lactic acid accumulations with increasing severity of deficiency. Conversion of glucose-one-C^{14} to $C^{14}O_2$ was only slightly depressed, but with increasing deficiency, erythrocyte oxidation of glucose-2-C^{14} to $C^{14}O_2$ decreased to only one-seventh the normal rate, and oxygen uptake was somewhat lowered. The addition of 50 to 100 μg of thiamine-HCl to each flask decreased the accumulation of pentose and increased the conversion of glucose-2-C^{14} to $C^{14}O_2$ toward normal rates. In vivo administration of 3 mg thiamine-HCl per week also reversed the deficiency aberrations.

These changes in erythrocyte oxidation of glucose in the presence of methylene blue are significant in that thiamine deficiency may be evaluated in humans with as little as 1 or 2 ml of blood using similar techniques.

M. K. Horwitt

The antimetabolites have been of value in the study of the action of various nutrients. Thiamine deficiency has been produced acutely by various substances, among which are pyrithiamine and oxythiamine. It seems likely that the antagonists interfere with the combination of cocarboxylase with the enzyme carboxylase.

Antivitaminosis B_1, Produced by Dietary Means and Use of Anti-Vitamins (Neopyrithiamin and Oxythiamin) in Rodents. L. De Caro, G. Rindi, V. Perri, and G. Ferrari. *Internat. Ztschr. Vitaminforsch.* 28: 252, 1958.

A study has been made of the course of avitaminosis B_1 in rats and mice including the tissue content of thiamine. Dietary avitaminosis can be accelerated and exaggerated by means of neopyrithiamine. The action of neopyrithiamine expresses itself mainly as an impoverishment of the tissues, especially the nervous system, in phosphorylated thiamine and also as an increased excretion of urinary thiamine. The effect of neopyrithiamine exceeds that of oxythiamine, and it is suggested that the two substances affect the action of thiamine in different ways. Authors

The reduction in glutamic-acid levels in thiamine deficiency may be the result of increased utilization of this factor by cerebral tissue, for which it is an important substrate.

The Metabolic Changes in Thiamine Deficiency as Reflected in the Individual Free Aminoacids in Tissues. V. Ferrari. *Acta vitaminol.* 2: 53, 1957.

Quantitative analysis for individual free amino acids showed that the level of these substances in the brain tissue is practically unaffected by partial inanition per se. In thiamine deficiency there was a 15 per cent reduction of the free glutamic acid level, but on the whole the remainder of the free amino acid pattern did not appear significantly affected by the lack of thiamine.

Author

Fulminating Beriberi. J. H. Baron and L. C. Oliver. *Lancet* 1: 354, 1958.

Beriberi is extremely rare in Britain; in its fulminating form it is almost unknown. A case is described of a 55-year-old woman who was under investigation in the hospital for an obscure peripheral neuropathy. About one month after admission she became suddenly ill with acute Wernicke's encephalopathy, Korsakov psychosis, and cardiac failure. She improved rapidly with vitamin B treatment but has not progressed beyond the state in which she was originally seen. Advanced gastric atrophy was also present.

F. E. Hytten

The dietary thiamine intake is recommended at the level of 0.5 mg per 1,000 calories of energy. A means for determining the dietary adequacy of thiamine as well as riboflavin is investigated in the following report.

Excretion of Thiamine and Riboflavin by Children. G. Stearns, L. Adamson, J. B. McKinley, T. Linner, and P. C. Jeans. *A.M.A. J. Dis. Child* 95: 185, 1958.

This report comprises 84 six-day studies and 45 four-day studies of 21 children (5 girls and 16 boys), who ranged in age from $4^3/_4$ to 13 years and in weight from 16 to 42 kg. The object was to determine the different amounts of those vitamins in foods being ingested by children and to estimate from the results obtained the requirements of children for thiamine and riboflavin. Each child in the original study was given in succession a basal diet and two experimental diets, wherein one food was substituted at two levels. Thiamine intake varied from 0.47 to 2.83 mg daily; riboflavin intake, from 0.79 to 3.23 mg daily. In addition, six children were given diets containing 0.35 mg or less of thiamine chloride daily until urinary excretion of this vitamin had apparently reached a minimum level or until it was deemed medically desirable to increase the thiamine intake.

The correlation between thiamine intake and urinary excretion was high (0.77 on the per diem and 0.71 on the per kilogram basis), demonstrating that thiamine in-

take is the major factor influencing urinary thiamine excretion. Correlation of urinary thiamine with intake per 1,000 cal was only 0.46. Children receiving 0.7 to 1.4 mg of thiamine daily excreted about 19 per cent of the intake in the urine. Urinary excretion of thiamine per gram of creatinine appears to be higher for children than for adults.

Urinary riboflavin varied directly with intake; the correlation coefficient was 0.85 on the per diem and 0.82 on the basis. These values show that riboflavin intake is the major factor regulating urinary excretion. Correlation between intake of riboflavin per 1,000 calories and total daily urinary excretion was so low that no statistical evaluation was attempted. Riboflavin produced by bacterial action in the gastrointestinal tract cannot be an important source of riboflavin for the child under the conditions reported here. No significant correlation was observed between the urinary riboflavin and nitrogen retention; average urinary riboflavin excretion exceeded 800 μg/g of creatinine.

The data from this study are interpreted to indicate storage of both thiamine and riboflavin in growing children given ample amounts of these vitamins. It is considered that a urinary thiamine excretion consistently at or above 20 per cent of the intake and urinary riboflavin excretion consistently above 40 per cent of the intake are evidence that intake has been ample for some time. A urinary thiamine 15 per cent or more of intake or urinary riboflavin 20 per cent or more intake is evidence of immediate adequacy of ingestion. Urinary excretion of less than 10 per cent of the intake of either vitamin is considered cause for concern. T. C. Panos

INTESTINAL-MALABSORPTION SYNDROME

The ingestion of the gluten protein fraction of several cereal grains, inluding wheat, rye, and oats, is responsible for the inability of certain patients to absorb fats and amino acids. The exclusion of these grains and products prepared from them has produced dramatic improvement in the clinical status in most patients with nontropical sprue. In adults, beer and ale must be omitted since they may contain cereal-grain residues.

The Effect of a Gluten-Free Diet on Fat, Nitrogen and Mineral Metabolism in Patients with Sprue. M. K. Schwartz, M. P. Sleisenger, J. H. Pert, K. E. Roberts, H. T. Randall, and T. P. Almy. *Gastroenterology* 32: 232, 1957.

Six patients with nontropical sprue responded dramatically to a gluten-free diet with corresponding improvement in intestinal absorption, the remissions being maintained for periods of eight months to three years. Care was taken that the gluten-free diet should exclude not only bakery products made with wheat or rye flour, but also all prepared foods containing wheat and wheat products as filler. Metabolic balance studies on two of the patients demonstrated that while on the gluten-free diet absorption of fat, nitrogen, sodium, potassium, magnesium, and phosphorus returned to normal. Calcium absorption was improved and its balance became positive, although urinary calcium did not increase, apparently because of skeletal remineralization. Two of these patients had previously been given cortisone, two had received folic acid, and two had been placed on a low-fat diet. None of these regimens provided the complete and sustained remission observed while the patients were on the gluten-free diet. When gluten was given to the patients in capsules without their knowledge, or the patients were placed upon a regular diet for brief periods, there was a mild recurrence of symptoms in some of the patients.

The authors feel as a result of this study that the gluten-free diet is the most satisfactory treatment for nontropical sprue. Their results were in contrast to those of previous workers who have obtained satisfactory clinical remissions in only approximately one-half of the patients with nontropical sprue. The success of this dietary regimen suggests to this group that sensitivity to gluten is a constant factor in nontropical sprue and that adrenocorticosteroids may owe their partial effectiveness to their sensitivity-suppressing property. Their results should encourage wider use of the gluten-free diet, and its evaluation by other groups. J. B. Hammond

The Effect of a Wheat-Gluten-Free Diet in Adult Idiopathic Steatorrhoea. J. M. French, C. F. Hawkins, and Nadya Smith. *Quart. J. Med.* 26: 481, 1957.

Earlier results of a gluten-free diet in the treatment of adults with idiopathic steatorrhea (nontropical sprue) have been less satisfactory than those in children with celiac disease. The authors report extensive observations from 22 patients, between 17 and 68 years of age, receiving this therapy. Sixteen patients recovered completely, as judged by clinical, hematologic, and biochemical findings. Five of these patients who returned to a normal diet had a relapse within a few days. The six patients who failed to respond to treatment either died or remain in a state of ill health. Improvement on this regimen is slower than in the child, sometimes taking more than six months, and treatment must be continued indefinitely. Failure to respond indicates a poor prognosis and raises the possibility of malabsorption disorders other than idiopathic steatorrhea.

W. H. J. Summerskill

Effect of a Gluten-free Diet in Idiopathic Steatorrhoea. A. Brown. *Brit. M. J.* 2: 337, 1957.

The value of a gluten-free diet has been well established in celiac disease, particularly in young children. In the present report the effect of such a diet on three older patients is described. One, a girl of 13, had had celiac disease for eight years and was brought into hospital badly malnourished and anemic; the second, a girl of 15, had been ill for about 10 years and was obviously underdeveloped; the third was a woman of 40 with steatorrhea for eight years, osteomalacic deformity, and

severe anemia. They are briefly described. All responded completely to the removal of gluten from the diet.

A gluten-free diet should be tried in all cases of steatorrhea, regardless of patient's age or duration of symptoms. F. E. HYTTEN

Gluten-Free Diets. R. F. Fletcher and M. Y. McCririck. *Brit. M. J.* 1: 299, 1958.

The discovery that wheat or rye "gluten" was the harmful agent in celiac disease represented a tremendous therapeutic advance, but the practical details of applying a gluten-free diet are often difficult.

In this paper details are given of gluten-free and gluten-containing foods together with some menus and suggested recipes for cakes and puddings made with gluten-free flour. Obviously this material cannot be abstracted, but it should be a very useful paper for every pediatrician to read. F. E. HYTTEN

The mechanism of gluten-induced malabsorption is entirely unknown. The correction of hypoproteinemia by dietary exclusion of gluten is an observation which may warrant wider investigation.

Wheat Gluten and Coeliac Disease. C. Alvey, C. M. Anderson, and M. Freeman. *Arch. Dis. Childhood* 32: 434, 1957.

It is now well-established that wheat gluten is the agent responsible for the symptom complex of celiac disease, but the mechanism of its action has not been clearly established. Two suggested hypotheses have been investigated in this study. One, that the syndrome is an allergic reaction to the gluten, was investigated by intradermal skin tests with gluten; the results were completely negative. The second, more popular theory is that the disease represents an intestinal enzyme deficiency. Digestion to the peptide stage appears to occur normally in celiac children, and other evidence suggests that a peptide-containing glutamine is the toxic fraction. "These features suggest that a specific mucosal peptidase, which might deaminate the peptide is absent from the small intestine," but it may also be that removal of glutamine peptides from the blood by the liver is at fault since the blood glutamine rises to a greater height in celiac than in normal children. F. E. HYTTEN

Hypoproteinaemia after Partial Gastrectomy Corrected by Gluten-free Diet. J. W. B. Forshaw. *Brit. M. J.* 2: 1020, 1958.

If nutritional disturbances follow partial gastrectomy they are usually concerned with the defective absorption of iron, fat, and the vitamin B complex; rarely and to a lesser extent nitrogen absorption may be affected. The malabsorption, particularly of fat, is improved by excluding gluten from the diet.

An unusual case is presented of a 47-year-old man who developed severe hypoproteinemia after partial gastrectomy together with some failure to absorb B vitamins. Fat absorption was good. Blood protein level fell to 4.6 g/100 ml (albumin 1.6 g, globulin 3 g). On a gluten-free diet the plasma protein rose over a period of about a month to normal levels and was maintained at this level as long as the diet was kept up.

F. E. HYTTEN

Idiopathic Steatorrhea Associated with Severe Hypoproteinaemia. J. W. B. Forshaw. *Lancet* 2: 720, 1957.

Impaired absorption of calcium, folic acid, vitamin B_{12} and iron is well known in steatorrhea, but impaired protein absorption sufficient to cause hypoproteinemia is rare.

The case is described of a woman, aged 31, whose main presenting sign was of gross edema. Her serum protein level was only 3.2 g/100 ml and fat balance over 5 days showed 89 per cent fat absorption. She had no anemia. The woman was given a gluten-free diet with characteristically satisfactory results for the steatorrhea and rapid restoration of serum protein levels.

F. E. HYTTEN

The glucose-tolerance test is a simple and effective means for distinguishing steatorrhea of pancreatic origin from that due to sprue.

The Value of the Oral Glucose Test in the Diagnosis of Pancreatic from Idiopathic Steatorrhoea. R. Gaddie, G. Thomas, N. Smith, and J. M. French. *Quart. J. Med.* 26: 121, 1957.

It is not always easy to distinguish clinically cases of pancreatic steatorrhea from the so-called idiopathic steatorrhea. The differentiation can be made on examination of duodenal secretion, but the test itself is tedious and the analysis takes considerable time.

The results of oral glucose-tolerance tests are given for 10 patients with pancreatic steatorrhea and 10 with idiopathic steatorrhea. They are described in detail, together with fat balance data.

The glucose-tolerance test provides a very clear distinction between the two types of steatorrhea. In all those of pancreatic origin it was impaired, four patients being frankly diabetic. In sharp contrast to this patients with idiopathic steatorrhea gave "flat" curves, none rising above 140 mg/100 ml. F. E. HYTTEN

The excellent studies from the Mt. Sinai Hospital of New York concerning the authors' experiences with the malabsorption syndrome are summarized. The success of steroid administration without emphasis upon dietary gluten exclusion suggests that the hormone may in some way interfere with the influence of the cereal protein upon intestinal absorptive processes.

Disturbances in Protein and Lipid Metabolism in Malabsorption Syndrome. D. Adlersberg, C. I. Wang, and E. T. Bossak. *J. Mt. Sinai Hosp. New York* 24: 206, 1957.

The laboratory evidences of disturbed protein and lipid metabolism in 95 patients with relatively severe idiopathic sprue are presented. Hypoalbuminemia was a common feature, the mean serum albumin concentration being 3.3 and ranging from 1.5 to 5.3 g/100 ml. In 16 patients with edema, serum albumin levels were lower than in the nonedematous group, averaging 2.4 g/100 ml. Two of the 16 patients had ascites in addition to edema. Their serum albumin concentrations were 1.7 and 1.9 g/100 ml. No abnormalities were noted in the serum globulin fraction.

Serum levels of total lipids, cholesterol, and phospholipids were depressed, the average values being 584 mg, 162 mg, and 203 mg/per 100 ml. Although these values usually rose when the patients were in remission, they often remained below normal.

Serum vitamin A and carotene levels were low during exacerbations of the disease. In patients in remission, levels of vitamin A and carotene were higher but absorption curves of vitamin A remained flat, indicating a persisting defect in absorption of this vitamin.

It is of interest that the Mt. Sinai series obtained a greater proportion of patients with hypoalbuminemia than was noted in a recent report from the General Hospital in Birmingham, England. The authors point out that this might be due simply to the greater severity of the sprue syndrome in their patients.

J. B. HAMMOND

Clinical Aspects of Malabsorption Syndrome (Idiopathic Sprue): Observations in 94 Patients. E. T. Bossak, C. I. Wang, and D. Adlersberg. *J. Mt. Sinai Hosp. New York* 24: 286, 1957.

The clinical findings of 94 patients with idiopathic sprue are summarized. Nearly all patients complained of diarrhea, weakness, and weight loss. Diarrhea was usually intermittent and rather watery; pale, bulky stools were often noted during exacerbations of the disease.

Five and three-tenths per cent of the patients had no diarrhea and were thought to have a latent or incomplete form of the disease. Abdominal discomfort, anorexia, nausea and vomiting, hemorrhagic manifestations, and tetany occurred in one-third to one-fourth of the patients.

Emaciation was the most common sign occurring in two-thirds of the patients. Abdominal distention, fever, hepatomegaly, hypotension, and clubbing of the fingers occurred in one-third to one-fourth of the group.

The bone marrow was studied in 30 patients and was normal in 36.7 per cent, megaloblastic in 33.3 per cent, and showed erythrohyperplasia in 20.0 per cent. The prothrombin time was prolonged in over two-thirds of the patients examined. Approximately two-thirds of the patients had hypocalcemia and an elevation of the serum alkaline phosphatase, and x-ray evidence of bone demineralization. The serum phosphorus level was below 2.5 mg per 100 cc in 28.3 per cent. Hypokalemia occurred in 16.7 per cent of patients and hypoglycemia in 12.2 per cent. Minor abnormalities in liver-function tests were noted in 21.4 per cent of the patients examined.

A flat oral glucose tolerance test was noted in 92 per cent. Depressed excretion of vitamin B_{12} as determined by the Schilling test was noted in 87 per cent of patients studied. An increase in fecal fat (above 15 per cent dry weight) was observed in 93.1 per cent of patients studied.

It was noted that among the 23 Puerto Ricans with tropical sprue included in this study, the symptoms were of shorter duration than the mean. Glossitis, macrocytic anemia, and hepatomegaly were more common, while tetany, hemorrhagic phenomena, and digital clubbing were rare. Osteomalacia was seen in only one patient in this group.

Treatment of patients of this series varied from a low-fat diet only to include liver extract, folic acid, and vitamin B_{12} to prolonged therapy with steroid hormones. A remission was obtained in 6.4 per cent of patients, full clinical control in 42.5 per cent, partial clinical control in 30.9 per cent, and no change in 5.3 per cent. Of the patients in this series 14.9 per cent died during the period of observation.

J. B. HAMMOND

Management of Patients with Malabsorption Syndrome. H. Colcher and D. Adlersberg. *J. Mt. Sinai Hosp. New York* 24: 380, 1957.

Details of therapy and management of patients with idiopathic sprue are presented. The dietary management used in the Mt. Sinai Hospital series was chiefly a low-fat, high-protein, high-carbohydrate (actually high monosaccharide) diet. The authors have had only limited experience with a gluten-free diet. Liver extract, folic acid, folinic acid, and vitamin B_{12} can produce striking hematologic responses. Iron therapy was given patients with microcytic, hypochromic anemia. In addition, vitamin K was required for the treatment of hemorrhagic manifestations. Hypocalcemia and tetany responded to large doses of calcium. Osteomalacia was found to be an indication for large doses of vitamin D and testosterone. Hypoproteinemia responded transiently to salt-free albumin or plasma, and over a longer period, to steroid hormones.

Prolonged steroid hormone therapy was carried out in 30 patients in this series. A clinical remission was observed in 28. Although a full remission or cure was not obtained in any patients in this series under steroid therapy, 20 were adequately controlled and able to lead nearly normal lives.

J. B. HAMMOND

The technique of peroral biopsy of the mucosa of the small intestine is an important adjunct to the investigation of disease in this difficultly accessible region.

Coeliac Disease with Atrophy of the Small-Intestine Mucosa. J. Sakula and M. Shiner. *Lancet* 2: 876, 1957.

A biopsy of the mucosa of the small intestine, taken by the oral route for what may be the first time, is reported for an 8-year-old boy with celiac disease.

There was villous atrophy similar to that found in idiopathic steatorrhea in adults. It is considered that these changes, which may be due to a hereditary trait, are possibly of primary importance in the etiology of the disease. F. E. HYTTEN

The Absorption of Glycine and Its Conversion to Serine in Patients with Sprue. C. E. Butterworth, Jr., R. Santini, Jr., and E. Perez-Santiago. *J. Clin. Invest.* 37: 20, 1958.

Because of the role of folic acid in the conversion of glycine to serine and because of the evidence that patients with tropical sprue are deficient in folic acid, it was postulated that impaired conversion of glycine to serine in such cases might lead to an accumulation of glycine in plasma, thus masking reduced absorption. Therefore, chemical determinations of plasma glycine, serine, and total amino acid nitrogen after glycine administration by mouth were carried out in 9 normal subjects, 8 patients with sprue in relapse, and 9 with sprue in remission.

The evidence indicated a slow rate of intestinal absorption and a delayed peak value in the untreated subjects compared with normals. Patients with sprue in remission had values intermediate between the two. According to the experiment as described, there was no evidence of impaired conversion of glycine to serine in sprue. However, there was some suggestion of an impairment of serine utilization. This was based on significantly higher levels of serine in the blood in untreated sprue patients. S. O. WAIFE

Excretion of Fluid in Malabsorption States. R. Misk, B. A. Scobie, and W. H. J. Summerskill. *Lancet* 1: 390, 1958.

There are a number of pointers to disordered water metabolism in idiopathic steatorrhea, including a failure of diuresis after an oral water load.

In the experiments reported here, 14 subjects with malabsorption syndromes (3 with idiopathic steatorrhea, 4 with regional ileitis, 1 with tuberculous enteritis, 1 with jejunal diverticulosis, and 5 with steatorrhea following gastrectomy) are compared with 19 healthy persons. In neither group was there any evidence of renal disease.

Both groups were given oral and intravenous water loads in the fasting and nonfasting states; in each case the subjects with malabsorption states showed impairment of diuresis. The degree of impairment was more closely related to the clinical severity of the condition than to any specific biochemical, radiologic, hematologic, or histologic change which could be measured, and it is suggested that disordered renal excretion is more important than malabsorption of water from the intestine. F. E. HYTTEN

ITEMS OF GENERAL INTEREST

Diet and Coronary Thrombosis: Hypothesis and Fact. J. Yudkin. *Lancet* 2: 155, 1957.

The simple hypothesis that the incidence of coronary thrombosis is closely correlated with the quantity of dietary fat or with a particular type of fat has been questioned on a number of grounds. Many epidemiologic data cannot be easily fitted to it and "as more and more of these awkward facts turn up, one begins to have the uneasy feeling that both the proponents and the opponents of a dietary hypothesis are quoting only those data which support their view."

In this lecture, Professor Yudkin brings many of the available data together and examines the picture. International statistics give no suggestion that mortality from coronary disease is closely related to either total fat intake or to the intake of any single type of fat. For example, the mortality rises slightly, from 57 to about 200 per 100,000, as the average fat intake in different countries rises from 16 to about 120 g daily. For fat intakes between about 120 and 150 g the mortality varies from about 200 to over 800. A similar lack of correlation applies to the other fats. The best correlation for a nutrient is found for sugar, suggesting that coronary thrombosis is related to higher living standards; this is supported by the relationship between coronary mortality and national income per capita.

Social class statistics within a country are difficult to interpret, but coronary mortality in Britain rises with increasing socioeconomic level; there are relatively small differences in dietary intakes, but the higher social classes have a slightly better diet with more butter and less margarine. Historically the secular changes in coronary mortality since 1928 show no obvious relationship to changes in the average fat intakes during those years. The best correlation illustrated is a close one between the coronary mortality and the numbers of radio and television licenses!

These findings are discussed broadly with the general conclusion that "relative over-consumption of food, associated with reduced physical exercise may be one of several causes of the disease." There are likely to be both predisposing and precipitating causes and some types of investigation which might be profitably undertaken to sort out the tangle are suggested.

This is an important paper in what has become one of the most overburdened sections of medical literature. It should be read in the original. F. E. HYTTEN

Prediction of Serum-Cholesterol Responses of Man to Changes in Fats in the Diet. A. Keys, J. T. Anderson, and F. Grande. *Lancet* 2: 959, 1957.

Although it is well known that lowering the fat content of the average American or West European diet reduces the serum cholesterol level, the fundamental

dietary differences which are important are still argued.

In this study, groups of 12 to 27 men were studied in calorie balance in dietary experiments controlled so that each man was maintained on a standard diet for four weeks and then for 2 to 9 weeks on each of from two to six diets differing in fat content (9–44 per cent of calories) and with an experimental fat usually representing about three-fourths of the total fat. Fats studied included butter fat, hydrogenated coconut oil, olive oil, cottonseed oil, corn oil, sunflower-seed oil, safflower oil, fish oil, and the mixed food fats of "ordinary American diets;" and fat intakes as a proportion of total calories were estimated as saturated, monoethenoid, and polyethenoid fatty acids.

Statistical analysis of the serum-cholesterol levels at the end of each dietary period yielded the least-squares multiple regression equation for the averages of groups of subjects: average change in mg total cholesterol/100 ml of serum = $2.74\Delta S - 1.31\Delta P$ for all fats except corn oil and hydrogenated coconut oil.

The equation overestimates by an average of 11 mg/100 ml the serum-cholesterol level on diets providing 20 to 30 per cent of calories from corn oil, but is satisfactory for hydrogenated coconut oil only if "saturated" is interpreted to mean fatty acids with more than 10 carbons. Another, less accurate formula, is derived using iodine numbers. The equations are more reliable for groups than for individuals.

"These experiments and their analysis offer no support for the suggestion that a deficiency of essential fatty acids produces the high serum-cholesterol levels characteristic of populations subsisting on luxurious American and Western European diets. Effective correction of these high serum-cholesterol levels involves a decrease in the most common fats in such diets and the secondary substitution of fats high in polyethenoid fatty acids."

The study is reported in very great detail.

F. E. HYTTEN

Weight Gain from Simple Overeating: II. Serum Lipids and Blood Volume. H. T. Anderson, A. Lawler, and A. Keys. *J. Clin. Invest.* 36: 81, 1957.

Caloric intakes of 20 schizophrenic men who were otherwise healthy were increased without changing physical activity. Diet was constant and adequate in vitamins and protein. Carbohydrate furnished two-thirds and fat one-third of added calories. As a result the proportion of calories due to fat decreased, although total fat intake was higher. Calories were thus increased 8 to 39 per cent for 20 weeks. On this regimen weight gain varied from 2.5 to 22.2 kg (average 0.5 kg/week). Total serum cholesterol increased 20 mg/100 ml during the first five weeks, but then leveled off, even though gain in weight continued. On the other hand, S_f 12–20 lipoprotein increased from the 10th to the 20th week, even though cholesterol was not changing at this time. There was some increase in circulating plasma and blood volume during the early part of the overeating period. The authors consider that these data support the thesis that serum cholesterol concentration is determined by the fat transport load per unit of circulation imposed on the blood.

M. J. OPPENHEIMER

Dietary Fat and Cholesterol Metabolism: Faecal Elimination of Bile Acids and Other Lipids. H. Gordon, B. Lewis, L. Eales, and J. F. Brock. *Lancet* 2: 1299, 1957.

Ten Bantu and Cape Coloured males aged between 19 and 57 were the subjects of a metabolic study; they were assumed to be physically normal after hospital treatment for a variety of diseases.

Each man was initially fed a basal low-fat diet of 1,800 to 2,500 calories, containing 6 to 9 g of fat and 85 to 93 g of protein.

A variety of fats were added to this diet: it was confirmed that the ingestion of the unsaturated fat sunflower-seed oil lowered the serum-cholesterol level and this could be maintained for at least 60 days. Hydrogenated coconut fat, fed under similar conditions, produced a sustained rise of the serum-cholesterol level. When both fats were fed together the serum-cholesterol level fell.

The capacity of sunflower-seed oil to lower blood cholesterol was not affected by heating in an open aluminum pot at 210°C for two hours.

The introduction of sunflower-seed oil into the diet sometimes produced a transient rise in fecal fat excretion, but in 9 of the 10 subjects normal fat absorption could be maintained for long periods with as much as 200 g of fat daily.

The fall in the serum-cholesterol level due to sunflower-seed oil was accompanied by a slight increase of neutral sterols and a considerable increase in bile acids in the feces. These changes were interpreted as indicating that sunflower-seed oil promotes the catabolism and excretion of cholesterol. F. E. HYTTEN

The Modification of Egg-Yolk Fats by Sunflower-Seed Oil and the Effect of Such Yolk Fats on Blood-cholesterol Levels. L. Horlick and J. B. O'Neil. *Lancet* 1: 243, 1957.

Hens were fed with 10 per cent sunflower-seed oil for eight weeks and their eggs collected. After ten days there was a six-fold increase in the di-unsaturated^{18} C fatty acids, due almost entirely to linoleic acid at the expense of oleic acid.

Two subjects were given these eggs to eat. Both had their serum cholesterol reduced by a low-fat diet before the trial period of egg feeding. In one the serum cholesterol rose slightly and then stabilized at 130 mg/100 ml (control 172 mg); in the other it continued to fall to about 100 mg. The serum cholesterol rose again after feeding with ordinary egg.

"Perhaps modification of foodstuffs may enable us to achieve the blood cholesterol levels now seen in populations which have low morbidity and mortality from atherosclerosis." F. E. HYTTEN

Serum-Lipids and Atherosclerosis among Yemenite Immigrants in Israel. M. Toor, A. Katchalsky, J. Agmon, and D. Allalouf. *Lancet* 1: 1270, 1957.

A comparison is made between a group of 55 Yemenite families who immigrated to Israel within the past five years and a group of 21 Yemenite families who had been in Israel more than twenty years. The long-established group had a diet containing a considerably greater proportion of fat and had higher plasma lipid and cholesterol values. The income of this group was about double that of recent immigrants and their families were smaller. The mortality from atherosclerosis (established clinically in most cases) is said to be four time greater in the older immigrant families.

There is considerable selection of cases on medical grounds for this experiment, and the validity of some of the comparisons may be doubted. Apart from adding another to the already substantial number of studies correlating fat intake and blood fat levels, this article raises more questions than it answers.

F. E. HYTTEN

Production of Hypercholesterolemia in the Rabbit by Infusion of Phosphatide (or Neutral Fat). M. Friedman and S. O. Byers. *Proc. Soc. Exper. Biol. Med.* 94: 452, 1957.

It has been demonstrated in the rat that a rapid rise in cholesterol occurs if there is a sustained elevation of plasma phospholipids or triglyceride produced by intravenous infusion. This may occur in the absence or the liver.

The present study was done to demonstrate changes in cholesterol levels of the rabbit after sustained hyperphospholipidemia. After 12 hours of continuous infusion there was a 320 per cent increase in plasma cholesterol, though no evidence of lipemia was detected (neutral fat not determined). After 24 hours the average cholesterol was increased 130 per cent. In another group of rabbits there was increase in cholesterol of 105 per cent and in phospholipids of 66 per cent after 10 hours of continuous infusion of fat emulsion (apricot oil). L. KINSELL

Atherosclerosis: V. The Serum and Plaque Lipids in Experimental Hypercholesteremia, with a Comparison of Plaque Structure and Lung Granulomas Caused by Cholesterol Esters. E. F. Hirsch, R. Nailor, and F. C. Bauer, Jr. *A.M.A. Arch. Pathol.* 64: 117, 1957.

Rabbits received intravenous injections of cholesterol oleate, a mixture of cholesterol oleate and cholesterol, or a mixture of cholesterol oleate and cholesterol stearate. The postprandial serum levels of the esterified fatty acids were recorded, and a comparison was made of the structure and composition of the lipid deposits in aorta, spleen, and lungs. The blood lipids of the hyperlipemic rabbits fed cholesterol had a disproportionately large content of cholesterol esters and free cholesterol. These lipids stimulated the formation of lipophages. With the exception of neutral fats, the lipid plaques in the aorta were mixtures reflecting components of the blood lipids, but their concentration in the tissues was considerably increased above those present in the blood plasma. Postprandial lipid deposits in liver, spleen, and lungs may be resorbed after the serum lipid levels return to normal. Fat emboli were observed in the lungs with formation of granulomas consisting of lipophages, a fibrillar stroma, and foreign-body giant cells, thus resembling lesions produced by intravenously administered embolic lipoid material. M. SILBERBERG

Experimental Xanthomatosis in the Rabbit: II. Changes in the Ground Substance. C. I. Wang, L. Strauss, and D. Adlersberg. *A.M.A. Arch. Path.* 64: 501, 1957.

Chinchilla gray male rabbits were fed a stock diet of rabbit chow supplemented with 1 g/day cholesterol for periods of from two weeks to ten months. Early changes observed in the animals thus treated consisted of an increase in the amounts of acid mucopolysaccharides demonstrable in the matrix of the corium, especially in the region of the hair follicles. After three to four months of treatment and later, aggregations of xanthomatous cells and extracellular deposits of cholesterol and cholesterol clefts were seen with clinical manifestations of xanthomatosis, while the colloidal iron reaction in the ground substance decreased. With the increased deposition of extracellular lipids the amount of acid mucopolysaccharides decreased. Similar but less striking changes were noted in the synovial membranes, tendons, and ligaments of bones and joints. Considerable individual variations in the degree of these xanthomatous changes and the time of their appearances were found to exist. M. SILBERBERG

The Morphology of Early Atherosclerotic Lesions of the Aorta Demonstrated by the Surface Technique in Rabbits Fed Cholesterol Together with a Description of the Anatomy of the Rabbit's Aorta and the "Spontaneous" Lesions Which Occur in It. G. L. Duff, G. C. McMillan, and A. C. Ritchie. *Am. J. Pathol.* 33: 845, 1957.

Since conventional histologic methods fail to demonstrate the earliest changes in atherosclerosis, a technique of surface examination of whole mounts of aortae was designed which allows microscopic studies of the first steps in atherogenesis. Young, adult, and old New Zealand rabbits were fed 93 g/day of a rabbit-food stock diet for various length of time. The experimental animals received the stock diet coated with 6 g corn oil supplemented with 1 g of powdered cholesterol. The shortest period of cholesterol feeding necessary to produce the earliest atherosclerotic changes in the aorta was from 4 to 48 hours. However, some rabbits showed no lesions after 30 days feeding the cholesterol diet. There was also no correlation between the duration of feeding of the experimental diet and the severity or type of the atherosclerotic lesion. The earliest changes were of focal nature. While microscopically the endothelial

lining of the aortae remained intact, small fat-staining droplets became visible in some intimal cells and occasionally also in the subendothelial mononuclear cells. As the lesion grew larger, more mononuclears containing larger amounts of fat-staining droplets appeared in the center and extended toward the periphery of the lesion, finally involving the fibrocytes that showed also finely dispersed fat globules. It is suggested that the fat-filled mononuclears enter the intima from the blood, because the largest fat-filled cells were found in the outermost layer of the intima, while those near the lining endothelium were small and contained only little fat. M. SILBERBERG

Resolution of Aortic Atherosclerotic Infiltration in the Rabbit by Phosphatide Infusion. M. Friedman, S. O. Byers, and R. H. Rosenman. *Proc. Soc. Exper. Biol. & Med.* 95: 587, 1957.

Male rabbits about six weeks old and weighing approximately 1,500 to 1,800 g received a diet of Purina rabbit chow supplemented with 1 per cent or 3 per cent cholesterol and 2 per cent or 4 per cent cottonseed oil. After three months hypercholesteremia developed; subsequently the supplements were withdrawn. Plasma cholesterol determinations were made before and during the feeding of the enriched diet. After three months, when the hypercholesteremia had disappeared, intermittent infusions of 15 ml of a 4 per cent suspension of phosphatides in 5 per cent dextrose were given. This procedure was repeated four to five times. The aortae were studied for atheromatous changes in rabbits not receiving and in those having received the infusion of phosphatides. The infusion of the phosphatide emulsion resulted in a marked resolution of the atherosclerotic infiltration and the cholesterol deposits in the aortae as compared with those animals that had not received the treatment with phosphatides.

M. SILBERBERG

The Effect of Chlorpromazine on Arterial Lipid Deposition in Rabbits After Cholesterol Feeding. S. L. Wilens and G. Gallo. *A.M.A. Arch. Path.* 64: 570, 1957.

Albino female rabbits weighing 2,100 to 2,600 g were fed a diet of rabbit food pellets supplemented with 1 g cholesterol per day for periods of 10 weeks. For an additional ten weeks the supplement of cholesterol was withdrawn. One batch of these rabbits received intravenous injections of 10 mg/kg chlorpromazine, while the remaining animals served as controls. After discontinuation of cholesterol feeding, blood cholesterol values returned to normal and visceral lipid deposits were resorbed, while arterial deposits of lipids persisted and even increased in severity. Administration of chlorpromazine accelerated the decline of the cholesterol levels and reduced slightly the extent of the atherosclerotic aortic lesions as compared to those seen in controls which had not been treated with the chemical.

M. SILBERBERG

The Reversibility of Atherosclerosis. G. C. Willis. *Canad. M.A.J.* 77: 106, 1957.

The resorption of atherosclerotic plaques was studied in this paper. In order to avoid the complications of the hyperlipemia usually associated with cholesterol feeding, ascorbic acid-deficient guinea pigs were used. In this species atherosclerosis occurs in ascorbic acid deficiency without cholesterol feeding. The animals were made ascorbic acid-deficient, and the resorption of the plaques was studied after the animals were fed ascorbic acid.

Results indicated that the diffuse lipids found in the early atherosclerotic lesions are resorbed rapidly. However, the advanced lesions are much more resistant. The lipid in this type of lesions becomes aggregated into forms of inert pools.

The effect of ascorbic acid feeding on atherosclerotic plaques in humans was studied in a few cases. Although the results were not conclusive the authors felt that the human may resorb plaques in a manner similar to that of the guinea pig. M. W. BATES

Comparison of Atherosclerosis in Guatemala City and New Orleans. C. Tejado and I. Gore. *Am. J. Pathol.* 33: 887, 1957.

Comparative pathologic anatomic studies were carried out on the incidence and severity of atherosclerosis of the aorta based on 616 unselected necropsies in New Orleans and 324 in Guatemala City. As compared to the New Orleans population the Guatemalans show more physical activity, have lower weights, and consume a diet low in fat and animal protein and high in vegetable protein. These dietary factors, partly due to the low living standard of the population, account as well for the fact that the Guatemalans fail to show the gain in weight common with advancing age in people of other countries and in particular in the United States. The average blood cholesterol values of the Guatemalans are substantially lower than those of the North Americans; the values for lipoproteins of the S_f 12–20 class and higher as measured in ultracentrifugation do not show differences as in the U. S. atherosclerotic individuals. The atherosclerotic lesions in the aorta found at necropsies were graded according to methods described, and the comparison between the two ethnic groups gave the following results: While in both groups the disease was present in its earliest stages after the second decade, the severity of the vascular lesions rose with advancing age. This rise was, however, significantly lower in Guatemalans than in North Americans. Of additional interest are the findings that after the age of forty, 51 in 316 atherosclerotic North Americans had myocardial infarcts as compared to 1 in 234 Guatemalans. M. SILBERBERG

Biological Studies of Dihydrocholesterol: II. Effect of Dehydrocholic Acid on Dihydrocholesterol-Induced Cholelithiasis in the Rabbit. E. H. Mosbach and M. Bevans. *A.M.A. Arch. Path.* 64: 162, 1957.

Male chinchilla or albino rabbits weighing 1.9 to 2.9

kg were maintained for three weeks on a diet of Purina laboratory chow pellets with supplements of 0.5 to 1 per cent dihydrocholesterol and/or 0.25 per cent dehydrocholic acid. The average cholesterol contents of serum, liver, and muscles were determined. The gallbladder was studied microscopically. In most animals fed dihydrocholesterol, cholecystitis and gallstones were found. Considerable amounts of dihydrocholesterol can be stored in the tissues, an effect which is intensified by dehydrocholic acid. The latter substance did not prevent the absorption of dihydrocholesterol from the gastrointestinal tract, but inhibited the changes in the gallbladder. The degree of inhibition depended upon the relative concentration of dihydrocholesterol and dihydrocholic acid, the maximum inhibition being obtained by a combination of 0.5 per cent dihydrocholesterol with 0.25 per cent dehydrocholic acid.

M. SILBERBERG

Vitamin B_6 and Reproduction. M. L. Ross and R. L. Pike. *J. Am. Dietet. A.* 33:42, 1957.

The effect of vitamin B_6 deficiency on fetal and maternal weight, maternal nitrogen retention, liver protein synthesis, serum protein, and nonprotein nitrogen concentrations in the rat are reviewed.

Results obtained from "nondepleted" and "depleted" animals are compared when the animals consumed one of five diets during gestation. These diets were pyridoxine-free or contained (1) 0.5 mg desoxypyridoxine/100 g ration or (2) 0.4, 0.8, or 1.2 mg B_6/100 g.

Good reproductive performance (criteria: maternal weight gains of over 100 g and average fetal weights of 5g or more) were recorded only for the nondepleted animals on the pyridoxine-containing rations. Groups on the three levels of vitamin B_6 showed no significant differences when comparisons were made of maternal weights within the depleted or nondepleted groups, but in all of five possible comparisons maternal weight gains of the nondepleted exceeded those of the depleted groups. Average weights of the young from depleted mothers on diets containing vitamin B_6 were as low as or lower than weight of the young from nondepleted animals maintained on desoxypyridoxine (8.4, 8.4, and 8.9 g vs. 9.8 g). The incidence of resorption was relatively high in all of the depleted animals and in the nondepleted animals on pyridoxine-deficient diets. Statistical analysis of data for litter size showed no significant differences in number of young produced by the nondepleted or depleted group.

Depletion of the maternal vitamin B_6 stores prior to mating and B_6 deficiency during pregnancy resulted in marked decreases in nitrogen retention. Food intakes, and consequently nitrogen and caloric intakes, were reduced in desoxypyridoxine-fed and vitamin B_6-free animals, so that direct comparisons are not valid.

Increases in ratios of liver weight and nitrogen content to body weight of depleted animals and desoxypyridoxine-supplemented nondepleted animals, when compared with appropriate controls, led the authors to conclude that there is a definite influence of vitamin B_6 on liver protein synthesis during pregnancy. It is further suggested on the basis of observed cessation of estrous cycles during B_6 depletion that this effect may be due to the influence of vitamin B_6-dependent enzyme systems or to hormonal change. Depletion of vitamin B_6 stores prior to mating resulted in serum protein concentrations significantly lower than those in nondepleted animals.

The author points out that changes recorded here for serum protein and nonprotein nitrogen concentrations in rats depleted of maternal vitamin B_6 stores prior to mating and subjected to vitamin B_6 deficiency during pregnancy were similar to those reported for complications of human pregnancy.

J. M. SMITH

Production of Xanthurenic Acid From Trytophan in Pregnancy and in Various States of Nitrogen Balance. W. W. Hawkins, V. G. Leonard, and C. M. Coles. *Am. J. Physiol.* 190:419, 1957.

Production of xanthurenic acid from tryptophan was studied in pregnant women, in pregnant rats, and in rats in vitamin B_6 deficiency and various states of nitrogen balance. Of eight women well advanced in pregnancy only one excreted excessive xanthurenic acid after a test dose of tryptophan, and this pregnancy was complicated by disease. The excessive excretion in this case was reduced by dosage with pyridoxine. Rats late in pregnancy and early in the postpartum period typically excreted abnormally large amounts of xanthurenic acid after test doses of tryptophan. The administration of extra vitamin B_6 or of other B vitamins had no effect. After the same level of dosage with tryptophan the excretion of xanthurenic acid by rats well advanced in vitamin B_6 deficiency was much higher than that by pregnant rats. No conclusive evidence was obtained that the production of xanthurenic acid from tryptophan is associated with the state of nitrogen balance as influenced by pregnancy, vitamin B_6 deficiency, or the intake of protein. Some of the experimental results suggested, however, that outside of vitamin B_6 deficiency it tends to be high when the retention of nitrogen is high.

AUTHORS

Study of Folic Acid and Vitamin B_{12} in Blood and Urine During Normal Pregnancy. H. Baker, R. Erdberg, I. Pasher, and H. Sobotka. *Proc. Soc. Exper. Biol. & Med.* 94:513, 1957.

Blood and urine levels of cyanocobalamine (vitamin B_{12}) and folic acid (PGA) were studied on a total of 47 pregnant women with uncomplicated pregnancies. Diets were unrestricted; vitamin supplement did not contain PGA or B_{12}. The median urinary B_{12} levels was 55 $\mu\mu$g/ml and the blood levels 193 $\mu\mu$g/ml (both values are low). The PGA content of urine and blood was elevated; the median was 19 $\mu\mu$g/ml (two to eight times as high as normal). Pregnancy exacts overwhelming demands on PGA and B_{12} stores.

L. KINSELL

Vitamin B_{12} and Iron Deficiencies in Anemia of Pregnancy and Puerperium. G. Izak, M. Rachmilewitz, Y. Stein, B. Berkovici, A. Sadovsky, Y. Aronovitch, and N. Grossowicz. *A.M.A. Arch. Int. Med.* 99:346, 1957.

Serial determinations of iron and vitamin B_{12} concentrations in the sera of women during pregnancy and the puerperium were made. Hemoglobin values below 10 g per ml were considered to indicate anemia. Of 500 women examined during pregnancy, 11.2 per cent were found to be "anemic." A similar percentage was found among 2,000 patients examined immediately following delivery. The majority of these women had immigrated to Israel from North Africa and the Near East. They were living under depressed economic conditions and had been under prolonged malnutrition states. The daily caloric intake was probably under 1,000 calories, and the total protein intake less than 40 g a day. From the total group, 100 patients were studied in detail. All complained of fatigue, palpitation, exertional dyspnea, and anorexia. Pallor and cheilosis were frequent. Moderate enlargement of the liver was also found.

Thirty of the 100 patients studied in detail had an iron-deficiency anemia manifested by hypochromia, low serum iron, and low mean corpuscular hemoglobin concentration. In eleven, the anemia was hyperchromic macrocytic, with a normal or high serum iron. In this latter group, the serum vitamin B_{12} concentration was as low as in pernicious anemia in relapse. This would be considered a megaloblastic anemia of pregnancy. The authors do not use the term "megaloblastic anemia" because of the small percentage of typical megaloblasts found in the marrow. In most of the anemic patients, there was a gradual fall in serum vitamin B_{12} levels during the last trimester. Fifty-nine patients showed the morphologic features of a dimorphic anemia, with both low serum vitamin B_{12} and low serum iron values. In most patients during the postpartum period there was a spontaneous hematologic improvement, with a gradual increase in both serum iron and serum vitamin B_{12} concentrations. Factors responsible for this finding were said to be malnutrition, frequent pregnancies, and the increased requirement during pregnancy.

This is a good study, in which Nature has set up the experimental conditions. S. O. Waife

Seasonal Incidence of Megaloblastic Anaemia of Pregnancy and the Puerperium. R. B. Thompson. *Lancet* 1:1171, 1957.

In the tropics most cases of megaloblastic anemia in pregnancy appear to be due to nutritional deficiency, but in temperate climates it has more usually been felt to be due to some "metabolic block."

In 100 cases of megaloblastic anemia from a group of English hospitals, the date of onset of the anemia, which could be calculated with reasonable accuracy to within one month, was determined. There is a very clear seasonal peak of incidence in the winter and early spring; for example, there were 14, 13, and 14 cases in January, February, and March, compared to 4, 5, and 7 cases in June, July, and August. Since the major sources of folic acid in the community studied were believed to be in fresh green vegetables, which are relatively more scarce in the winter, it is suggested that dietary deficiency is at least a contributory cause of the anemia. F. E. Hytten

Folinic Acid in Megaloblastic Anaemia of Pregnancy. J. M. Scott. *Brit. M. J.* 2:270, 1957.

The frequency of occurrence of megaloblastic anemia of pregnancy in well-nourished communities is not known, but it has become clear during recent years that it is much more common than was earlier believed, the incidence being strongly correlated with the assiduity with which its diagnosis is sought. The advent of folic acid has revolutionized the treatment of what was once often an extremely refractory, although self-limited condition.

Treatment of 19 cases is reviewed here; 17 were diagnosed before delivery. Thirteen required sternal marrow examination for their diagnosis; a brief clinical summary is given. Most of the women were treated by intramuscular injections of folinic acid beginning with 12 mg on the first day and 6 mg daily thereafter. Treatment was suspended when the reticulocyte response was maximal: this commonly occurred on the eighth day, after about 50 mg had been given. Three women had oral treatment, an initial dosage of 10 mg followed by 5 mg daily. Details of the recovery are not given but all were presumably satisfactory. F. E. Hytten

Clinical Significance of Weight Trends During Pregnancy. A. M. Thomson and W. Z. Billewicz. *Brit. M. J.* 1:243, 1957.

Accurate weight records during pregnancy were analyzed for 4,214 primigravidae not subjected to weight regulation. It was confirmed that the average rate of gain is higher in those who develop preeclampsia and the incidence of preeclampsia rises as average weight gain increases. This fact has little predictive value for an individual case.

The incidence of prematurity (birth weight 2,500 g or less) is high where maternal weight gains are particularly low, falls as the weight gain increases, and rises again in association with preeclampsia in the highest weight gains.

"The most favourable outcome of pregnancy—in terms of pre-eclampsia, prematurity and peri-natal death, is associated with a moderate rate of weight gain, at least throughout the second half of pregnancy." A gain of about one pound weekly during the second half of pregnancy is suggested as a sound and realistic average at which to aim. The rigorous dieting which has been advocated is thought to be unjustified and harmful. F. E. Hytten